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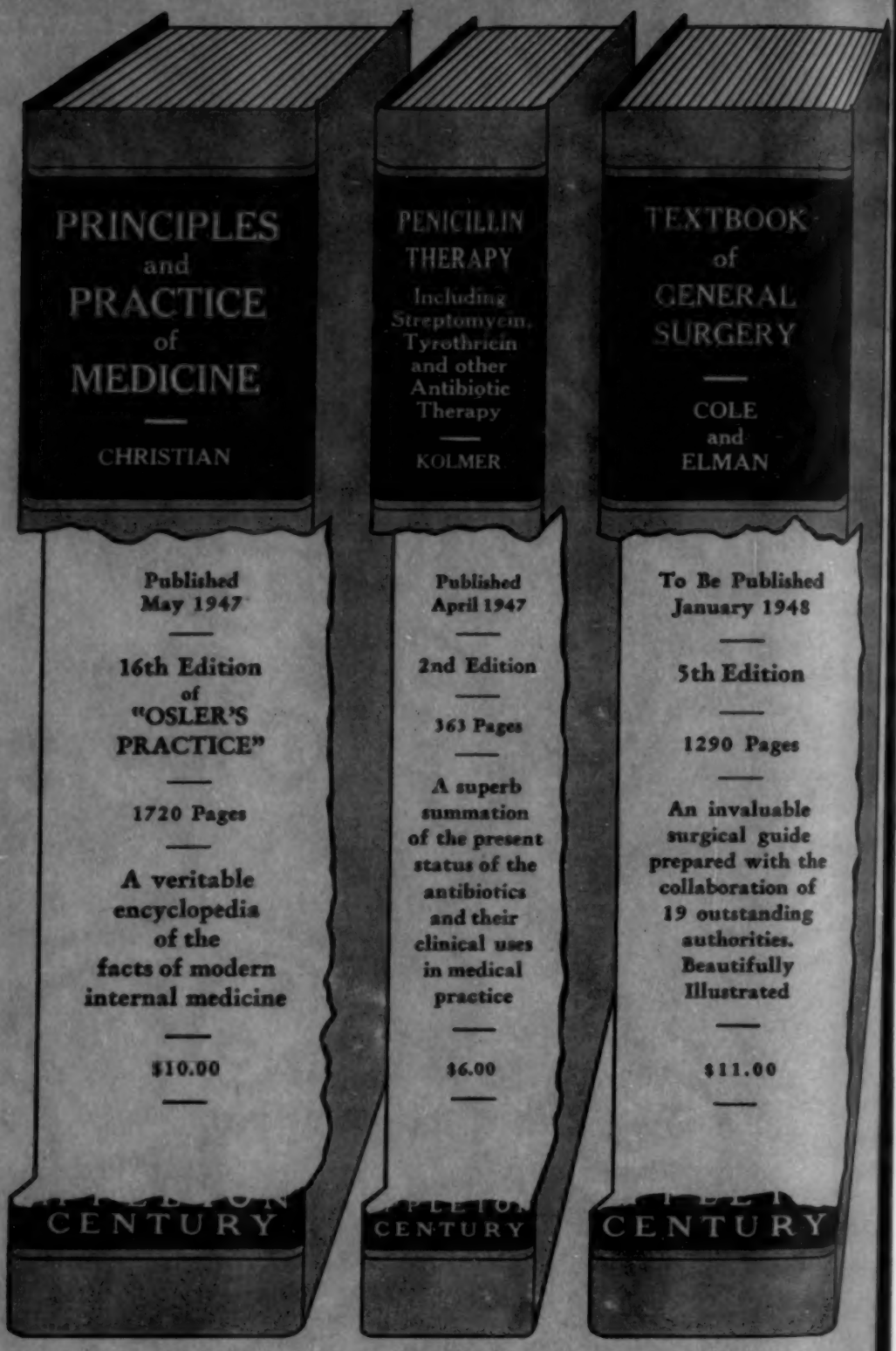

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ANNALS OF
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VOLUME 27 NOVEMBER 1947 NUMBER 5

HYPERVENTILATION: ANALYSIS OF CLINICAL SYMPTOMATOLOGY *

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HYPERVENTILATION is a common enough occurrence in clinical practice to justify further study of this phenomenon. Although the symptoms of hyperventilation are well known they are often overlooked because patients seldom complain of overbreathing, per se, and seldom exhibit tetany, the best known, but least common manifestation. Most often hyperventilation is psychogenic in origin. Thus, it may occur as a more or less non-specific reaction to the experience of terror, extreme anger, severe pain, or other intense emotions in essentially healthy individuals or it may be a symptom of neurosis. It occurs quite frequently during real anxiety and in the anxiety attacks of anxiety neurosis where it represents a physiologic concomitant of the anxiety. Physiologically, it serves the purpose of preparation for fight or flight, permitting prolonged physical exertion and even breathholding. A sensation of suffocation or smothering is a common occurrence during anxiety and may give rise to overbreathing of which the patient is unaware. In other instances, hyperventilation represents an hysterical conversion symptom, effecting the relief of an emotional tension in a more symbolic way. In such instances the overventilation may represent the expression of a repressed wish for sexual intercourse, or repressed hostility. Both mechanisms may be seen in the same patient.

Hyperventilation may also be observed during encephalopathies of a variety of causes and as a response to certain drugs, notably the salicylates.[1] And finally, hyperventilation is of practical significance at high altitude,

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where the physiologic effects of anoxia provoke overbreathing through reflex mechanisms.

Symptomatology: The symptoms developing during hyperventilation are much the same regardless of the etiology and may be reproduced in any person by voluntary hyperventilation. They include numbness and tingling of the hands, feet, and face; buzzing in the head; varying degrees of reduction in the level of consciousness, described as dizziness, light-headedness, giddiness or faintness; blurring of vision; dryness of the mouth; stiffness of the muscles and tetany. When there is reduction in the level of consciousness there is often release of other neurotic patterns, such as increased anxiety, panic, weeping, and various hysterical reactions. As anyone who has tried it can testify, hyperventilation is an exceedingly fatiguing activity and many patients who experience involuntary hyperventilation complain of severe fatigue and exhaustion.

The hyperventilating patient most often complains of fainting, convulsions or of attacks of breathlessness or smothering. Many of the latter type patients believe they have heart disease. Few patients are aware of overbreathing, though some will note excessive sighing or yawning. Among the patients who complain of "spells" careful history will usually reveal that numbness, tingling, lightheadedness, giddiness, blurring of vision, and sometimes a sense of breathlessness will precede the actual loss of consciousness by several minutes. Often the patients do not fall but experience a sense of impending loss of consciousness for some minutes. Some patients describe sensations of unreality or floating as the level of consciousness is reduced. These symptoms may occur in any position, and may continue for long periods of time, fluctuating in intensity as periods of hyperpnea alternating with periods of relative apnea. The longer the hyperventilation continues the more likely is tetany to appear, with its subjective symptoms of stiffness and cramping of the extremities.

In the literature it has been generally assumed that these various symptoms are of the same origin. It will be one purpose of this report to demonstrate that although alkalosis is the common denominator there are two more or less unrelated groups of symptoms, one related to the reduction in consciousness and one related to tetany. That is, some symptoms are central and some peripheral in origin.

The symptoms can always be reproduced by voluntary hyperventilation, although we have found that they may be modified in a number of ways. In general, the length of time that a person can carry out voluntary hyperventilation continuously is determined by one of three factors: loss of consciousness upon which the subject generally stops breathing involuntarily, resuming as the level of consciousness returns; tetany, which eventually limits the motion of the respiratory musculature; and fatigue. As is well known, a prolonged period of involuntary apnea may follow a period of hyperventilation.

Methods and Material: Medical students and staff members, all between the ages of 20 to 35 years, volunteered for these experiments. In addition, patients with this syndrome have been studied. The subjects were instructed to hyperventilate maximally for the designated period of time during which observations were made.

Bipolar fronto-occipital electroencephalograms were obtained by means of a Grass 3-channel instrument. The mean frequency of the brain waves was determined for successive 10 second periods by the method described in previous publications.[2, 3] The number of waves per second interval in 10 second intervals was counted, and from this a mean frequency for each 10 second period was calculated. This yielded a very satisfactory quantitative estimate of the progressive frequency changes during hyperventilation and provided more information than did the determination of a frequency spectrum for the whole period of hyperventilation.[2] Another method of expression was to calculate the mean frequency for the entire period of hyperventilation. Because of the greater accuracy of analysis, subjects were selected whose control records showed a high percentage of countable frequencies.

Blood sugar was determined by the Folin-Wu colorimetric method.

The effects of varying oxygen tensions were studied by hyperventilating at ground level (747 mm. Hg) and at a simulated altitude of 16,000 feet (412 mm. Hg) in the decompression chamber and by hyperventilation with 10 per cent oxygen–90 per cent nitrogen mixture inhaled through a Bulbulian type 14 demand mask modified for constant flow. The mask was equipped with a large balloon as a reservoir and the rate of flow was kept such that the rubber bag never collapsed. Each gas mixture was breathed for 10 minutes before hyperventilation was begun and 20 minutes were allowed for recovery from each period of hyperventilation. The order in which the different gas mixtures and different altitudes were tested was varied.

The effects of posture were tested on the tilt table. Pulse was recorded with the electroencephalograph. The subject stood motionless for from 15 to 30 minutes before hyperventilating to rule out any postural hypotension.

The level of consciousness was determined by presenting the subject with three objects to remember and a problem of multiplication to carry out during the last 30 seconds of a three-minute period of hyperventilation. As soon as the hyperventilation period was completed the subject was asked for the test material. One point was allowed for each correct response, giving a maximum score of six and a minimum of zero (no awareness that any test was given or no memory of any of the tests).

The effects of nitroglycerine, amyl nitrite, nicotinic acid, and calcium chloride were tested during successive periods of hyperventilation, on the same subjects, allowing 20 minutes for recovery between each experiment. Calcium chloride was given last.

Results

1. *Rate of Change in Arterial Blood During Hyperventilation.*

The changes in the arterial blood constituents will be discussed in more detail in another paper.[4] However, brief comment on the rate of change of the CO_2 content and tension and of the pH of blood during vigorous hyperventilation is pertinent at this time. The greatest part of the change in arterial CO_2 content is accomplished in the first 30 to 60 seconds of hyperventilation. The changes in CO_2 tension and in pH are also more rapid during the first 30 to 60 seconds, but less so than the rate of change of the CO_2 content. A single deep inspiration and expiration will reduce the CO_2 content by 5 to 7 volumes per cent and the CO_2 tension by 7 to 16 mm. Hg.[5] After the first minute, continued vigorous hyperventilation will lower CO_2 content only slightly. With different rates of hyperventilation, the rate of fall of CO_2 changed slightly but the eventual degree of reduction was about the same. These points are amply illustrated in the tables and charts of the papers referred to.[4, 5]

2. *Correlation Between Slowing of the Electroencephalogram and Level of Consciousness.*

When the level of consciousness was determined by testing the subjects' memory and ability to calculate during the last 30 seconds of a 180 second period of hyperventilation, it was found that there was a close correlation between the degree of reduction of awareness and the degree of slowing of frequency of the electroencephalogram. These results are illustrated in table 1 and figure 1, which also demonstrate the electroencephalographic frequency change during hyperventilation at varying oxygen tensions. In general, it was found that marked reduction in consciousness occurred when the electroencephalographic mean frequency was reduced to less than 5.0 cycles per second. If the subject was not unconscious at 150 seconds when the test of awareness was administered there was some tendency for depth of ventilation to diminish and electroencephalographic mean frequency to rise as the subject tried to concentrate on the task. Sometimes, when unconscious, the subject stopped breathing involuntarily.

Subjectively the symptoms described were essentially the same as those described by patients. However, it was of interest that when reduction in consciousness was marked the subject usually had no memory afterwards of having lost consciousness, merely feeling that the period of hyperventilation had been shorter than usual. In general, the more marked the reduction in consciousness, the less were the numbness and tingling and the less likely was tetany to appear. Usually if considerable slowing of the electroencephalogram and reduction in consciousness had not appeared by the end of three minutes of vigorous hyperventilation it was unlikely to appear, and the longer hyperventilation continued, the more likely was tetany to develop. None of the subjects fell while unconscious.

TABLE I

Electroencephalographic Mean Frequency Changes at Varying Oxygen Tensions; Correlation between Frequency and Level of Consciousness

Name	Gas Mixture	Electroencephalographic Mean Frequency Change during Hyperventilation																Blood Sugar mg. %	Level of Awareness 150–180 sec. (0–6)
		Time of Hyperventilation in Seconds																	
		Resting	30	40	50	60	70	80	90	100	110	120	130	140	150	160	170	180	
H. F.	10% O_2	9.3		7.8	7.7		5.3		5.0		4.3		4.1		5.4		3.4	4.2	74	2
	Air	9.4	8.2		8.3		6.7		6.1		5.7		5.0		4.5		4.0	5.4	71	2
	100% O_2	9.9	9.4			9.1			8.5		7.6		7.2		5.7		7.1	6.9	75	6
J. N.	10% O_2	9.9	9.3		9.0		7.7		6.9		5.1		3.9		6.3		7.3	6.6	86	5
	Air	11.1	10.6		10.9		10.2		9.0		7.6		7.5		5.9		6.8	8.3		6
	100% O_2	10.9	10.3		10.2		10.0		9.9		9.2		8.2		7.5		7.5	8.4	81	6
R. R.	10% O_2	10.1	9.8		9.0		7.5		6.2		5.5		5.1		3.4		3.7	2.8	72	0
	Air	10.4	10.0		10.1		8.2		5.8		4.5		3.5		3.0		4.5	3.4	73	0
	100% O_2	10.5	10.5		10.3		9.9		9.4		6.6		6.4		5.2		6.4	6.3	77	3
M. F.	10% O_2	11.1	9.9			7.3	4.7		4.4		3.5		3.5		3.6		3.4	5.1	81	1
	Air	11.1	10.6				9.5		8.3		6.3		5.6		5.3		7.9	6.0	86	3
	100% O_2	11.1	10.8		10.4		10.0						9.0		8.5		9.3	9.7	86	6
H. L.	10% O_2	9.3	9.1		8.9		9.1				8.8		8.9		8.4		8.9		96	3
	Air	9.6	9.5		9.5		9.4		9.5		9.1		9.4		8.8		8.7		96	4
	100% O_2	9.7	9.7			9.9		9.5		9.2			9.5			9.1			103	5

TABLE I (Continued)

Name	Gas Mixture	Electroencephalographic Mean Frequency Change during Hyperventilation																Blood Sugar mg. %	Level of Awareness 150–180 sec. (0–6)
		Time of Hyperventilation in Seconds																	
		Resting	30	40	50	60	70	80	90	100	110	120	130	140	150	160	170	180	
M. S.	10% O_2	11.7	11.3		10.7		9.4		8.3		6.9		7.5		7.8		9.9		6
	Air	11.7	11.9		11.4		11.7		11.3		11.3		11.2		10.6		10.8		6
	100% O_2	11.7	11.5		12.0		11.4		11.8		11.6		11.6		11.6		11.9		6
M. L.	10% O_2	8.8	8.9		8.9		8.4		7.3		5.0		4.6		4.4		5.5	6.5	60	
	Air	9.1	9.2		8.9		9.0		8.6		8.4		8.5		7.8		7.8	7.9	62	
	100% O_2	9.4		9.6			9.6		9.3		9.1		9.2		8.9		9.1	8.8	58	
W. S.	10% O_2	10.3	9.8		9.8		9.5		9.0		8.8		8.5		8.6		9.5	9.6	81	6
	Air	10.4	10.1		10.2		10.1		10.1		9.5		9.8		9.4		10.4	10.0	75	6
	100% O_2	10.6	10.2		10.3		10.1		10.3		10.2		10.3		10.0		9.9	10.3	76	6
W. P.	10% O_2	10.0	9.0		8.9		7.5		4.8		3.3		4.1		2.9		3.3	2.6	75	0
	Air	10.2	9.1		9.1		8.0		7.4		6.1		5.2		3.9		3.1	7.0	76	3
	100% O_2	10.0	9.5		9.4		9.2		8.0		9.0		8.3		7.7		7.6	7.3	85	5
H. K.	10% O_2	9.6	8.9		8.5		8.1		7.9				7.6		7.5		7.7	7.7	90	4
	Air	10.0	9.8		9.8		9.2		8.9		8.6		8.2		8.7		8.2	8.1	80	4
	100% O_2	10.3	9.8		9.9		9.5		9.7		9.3		9.7		9.5		9.5	9.5	78	6

Reduction in consciousness during hyperventilation had already been noted by Davis and Davis [6] who also observed a correlation with the appearance of delta waves. These results are also consistent with earlier studies of delirium in which it was demonstrated that the degree of reduction in consciousness in the acutely delirious patient correlated well with the degree of slowing of the electroencephalogram.[7]

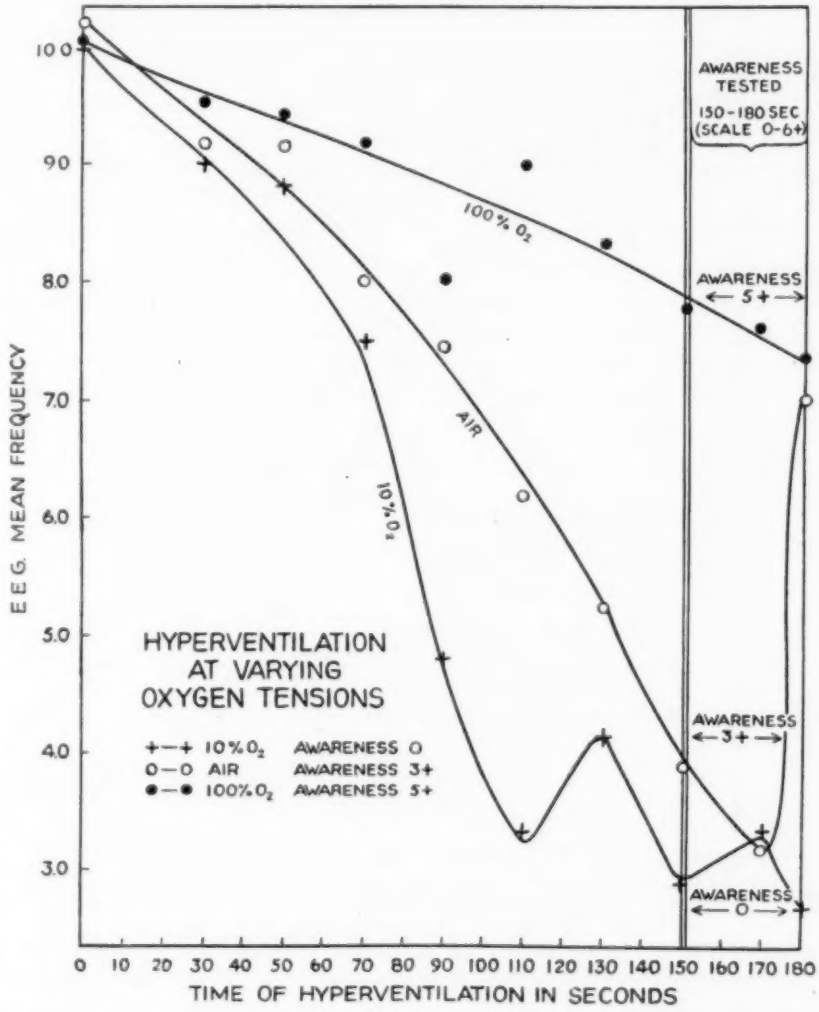

FIG. 1. E.E.G. mean frequency changes during hyperventilation at different oxygen tensions. Correlation with level of awareness.

3. *Factors Influencing the Degree of Slowing of the Electroencephalogram.*

Having established a correlation between the slowing of the electroencephalogram and level of consciousness, it becomes of importance to

delineate some of the factors influencing the amount of slowing during comparable degrees of acapnia. Repeated studies of arterial blood on the same subject during hyperventilation indicate that a coöperative subject achieves approximately the same degree of reduction in arterial CO_2 each time.

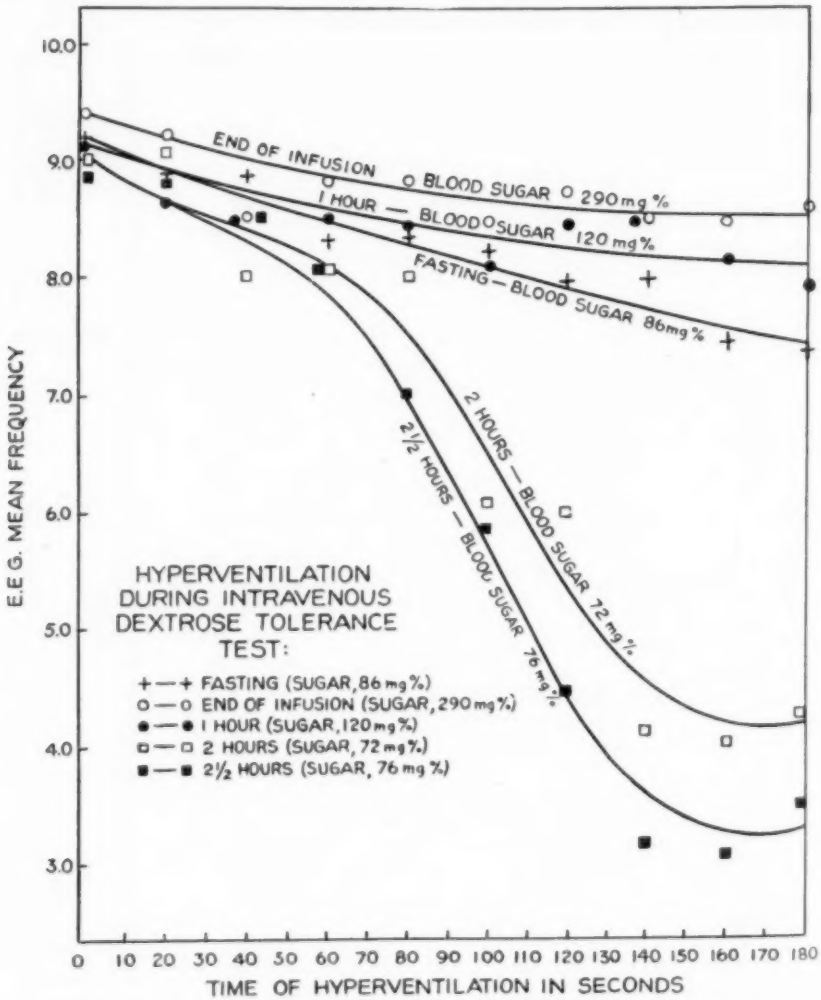
E.E.G. MEAN FREQUENCY
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
END OF INFUSION O BLOOD SUGAR O 290 mg %
1 HOUR — BLOOD SUGAR 120 mg %
FASTING — BLOOD SUGAR 86 mg %
2 HOURS — BLOOD SUGAR 72 mg %
2½ HOURS — BLOOD SUGAR 76 mg %
HYPERVENTILATION DURING INTRAVENOUS DEXTROSE TOLERANCE TEST:
+ — + FASTING (SUGAR, 86 mg %)
O — O END OF INFUSION (SUGAR, 290 mg %)
● — ● 1 HOUR (SUGAR, 120 mg %)
□ — □ 2 HOURS (SUGAR, 72 mg %)
■ — ■ 2½ HOURS (SUGAR, 76 mg %)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180
TIME OF HYPERVENTILATION IN SECONDS

FIG. 2. E.E.G. mean frequency change at different blood sugar levels.

(a) *Individual Differences:* When other factors are controlled there still is a considerable difference among normal individuals as regards the ease with which slowing of the electroencephalogram develops during hyperventilation. However, all subjects seem to respond in the same direction to the various known factors which influence electroencephalographic frequency during hyperventilation. The factors concerned in this individual variation

have yet to be established. They do not appear to be related to the character of the resting electroencephalogram.

(b) *Age:* The degree of slowing is greatest in children and young adults, decreasing with age and levelling off after about age 35 years.[8] The younger patient is thus more likely to develop disturbance in consciousness during hyperventilation.

(c) *Rate of Hyperventilation:* The rate at which arterial CO_2 is reduced seems to be of importance. Although a wide range of hyperventilation rates will reduce the arterial CO_2 tension to about the same level, the more rapidly the CO_2 is reduced the greater the slowing is likely to be.[4]

(d) *Blood Sugar:* The discovery that there was a correlation between the degree of electroencephalographic slowing during hyperventilation and the level of blood sugar was made simultaneously by a number of observers and has been the subject of many reports.[9] In figure 2 are illustrated the progressive electroencephalographic mean frequency changes at various points during an intravenous dextrose tolerance test. It will be noted in the data obtained on this subject that at the high blood sugar levels the rate of slowing during three minutes of hyperventilation was slight, while at the lowest blood sugar levels (72 and 76 mg. per cent) the slowing was marked. In

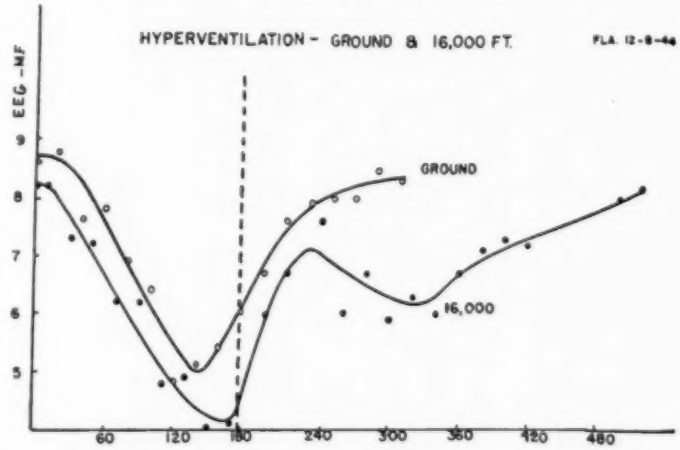

FIG. 3. Delay in recovery at 16,000 feet as compared to ground level.

general it has been found that significant slowing may be produced in the electroencephalogram of any normal individual if the blood sugar is reduced low enough, while blood sugar of 130 mg. per cent or higher will serve to eliminate significant slowing in most individuals. The intravenous injection of dextrose was not found to modify in any way the acid base balance of arterial blood during hyperventilation.[2]

With lower blood sugars where there is greater slowing of the electroencephalogram there is greater reduction in consciousness; with high blood sugar the subject can hyperventilate for longer periods and tetany is more likely to develop.

TABLE II

Electroencephalographic Mean Frequency Change on Ground and at Simulated Altitude of 16,000 Feet During Hyperventilation and Recovery

Name	Experiment	Electroencephalographic Mean Frequency Change — Time in Seconds																				Blood Sugar mg./100 c.c.	Comment
		Control	30	50	70	90	110	130	150	170	190	210	230	240	300	360	420	480	540	600	660	720	
Fl.	Ground	8.6	8.8	7.6	7.8	6.9	6.4	4.8	5.1	5.4	6.0	6.7	7.6	7.9	8.5	8.6							70	H.V.—180″
	16,000 ft.	8.2	7.3	7.2	6.2	6.2	4.8	4.9	4.0	4.1	4.8	6.0		7.6	5.9	6.7	7.2	8.0	8.0				60	H.V.—180″
M. L.	Ground	9.9	10.4	10.0	9.9	8.6	8.6	8.5	7.3	4.2	3.9	5.9	2.7	3.4	6.6	7.5	9.3	9.1	9.7					H.V.—240″
	16,000 ft.	8.6	8.9	8.3	7.0	6.5	5.3	4.5	4.8	3.4	3.6	4.4	3.1	5.4	6.3	5.5	6.3	6.5	7.6	7.8	8.3	8.6		H.V.—240″
Fr.	Ground	9.9	10.0	10.0	8.9	9.2	9.0	7.8	4.1	5.6	5.6	9.2	9.4	10.1									95	H.V.—180″
	16,000 ft.	9.8	8.4	8.7	6.6	4.6	5.6	4.6	3.7	3.5	2.6	3.0	7.2	6.2	7.2								95	H.V.—180″
N.	Ground	10.3	9.7	9.7	8.1	6.0	6.0	5.0	5.7	6.5	6.1	9.3		9.1	9.7								93	H.V.—180″
	16,000 ft.	10.0	8.8		7.6	7.3	5.5		6.4	3.7	6.0	6.2	7.2	7.4	7.2	6.2	8.7	8.7					94	H.V.—180″

TABLE III

Effect on Electroencephalogram at Change from Air to 100 Per Cent Oxygen During Hyperventilation

Name	Experiment		Time in Seconds																				Sugar mg./100 c.c.	Comment
			Control	30	60	90	120	150	180	210	240	270	300	330	360	390	420	450	480	510	540	570	600		
F.	Air	EEG.M.F.	9.7	9.5	9.0	9.2	8.7	8.7	6.6	7.0	6.6	5.9	6.6	8.2	6.7	7.6	5.8	6.1	6.6	6.6	5.6	5.7			
	Air 120 sec. then 100% O_2	EEG.M.F.	9.8	9.8	9.2	8.3	8.1	8.6	8.3	8.5	7.7	8.5	8.2		8.4		7.8	8.3	8.4	8.3		8.8			
Sh.	Air	EEG.M.F.	9.8	9.8	9.8	9.1	8.8	8.5	7.8	6.5	7.5	8.6	7.6	7.8	8.4	7.7								64	Tetany 4+
	Air 120 sec. then 100% O_2	EEG.M.F.	9.5	9.3	9.2	8.6	8.5	8.5	8.2	8.9		8.8	8.8	8.6	9.1	8.9								58	Tetany 4+
Sch.	Air	EEG.M.F.	10.2	9.6	9.6	9.1	8.8	8.9	8.6	8.0	7.5	6.4	7.0	5.7	6.5	7.1	6.0	6.0	6.0	6.1	4.2	3.9	4.1	72	
	Air 120 sec. then 100% O_2	EEG.M.F.	9.9	9.5	9.2	9.0	8.0	8.1	7.7	8.0	7.0	6.6	6.6	6.3	6.0	6.9	5.5	6.6	6.9	6.2	6.2	6.3	6.4	69	Hyperventilation more vigorous

(e) *Oxygen Tension of Inspired Air:* The relationship between the degree of electroencephalographic slowing and the oxygen tension of the inspired air is illustrated in tables 1 and 2 and figures 1 and 3. The slowing of the electroencephalogram was most marked with 10 per cent oxygen–90 per cent nitrogen mixture (table 1) and at simulated altitude of 16,000 ft. (412 mm. Hg) (table 2) breathing air, and least marked when inspiring 100 per cent oxygen. Also, the rate of return to control frequency was much slower at 16,000 ft. (412 mm. Hg) than at ground level (747 mm. Hg) (table 2) (figure 3). When 100 per cent oxygen was substituted after hyperventilation for two minutes with air, further slowing of the electroencephalogram was inhibited (table 3). The amount of slowing and of change in consciousness at high altitude or with low oxygen mixtures could not be accounted for on the basis of the effects of anoxia alone. The effect of this degree of anoxia on the electroencephalogram has already been studied and found to be slight as compared to the effects noted here.[3]

That hyperventilation could be carried out more comfortably with oxygen was first noted by Hill and Flack in 1910.[10] Davis and Wallace made similar observations.[9b]

(f) *Posture:* Slowing of the electroencephalogram during hyperventilation is greater in the erect position as compared to the recumbent. This has already been reported elsewhere[2] and is illustrated in table 4 and figure 4. Table 4 shows the mean frequency for a 180 second period of hyperventilation in both positions (4 subjects, 10 experiments) and the maximum pulse and minimum blood pressure during hyperventilation in each position. The increase in slowing is not correlated with any consistent fall in blood pressure in the erect as compared to the recumbent positions and hence cannot be accounted for on the basis of hypotension and a related decreased cerebral blood flow. However, the acceleration in pulse rate during hyperventilation was consistently greater in the erect position, the heart rate exceeding 130 per minute in four of the 10 experiments. The maximum pulse rate during hyperventilation in the erect position was 156 per minute; in the recumbent position, 126 per minute.

This correlation between heart rate and increased slowing of the electroencephalogram is consistent with the findings of Darrow[11] who observed tachycardia to be more pronounced among the subjects with more marked slowing.

(g) *Effects of Amyl Nitrite, Nitroglycerine, and Nicotinic Acid:* Because Schwab has stated that amyl nitrite, by its action as a cerebral vasodilator, eliminates the slow activity of hyperventilation it was thought pertinent to check this observation.[12] Two subjects were given amyl nitrite by inhalation and nitroglycerine sublingually while recumbent. After allowing 20 minutes to recover from a control hyperventilation, each drug was given at 20 minute intervals in separate experiments and the hyperventilation begun after objective evidences of drug effect had developed. As can be

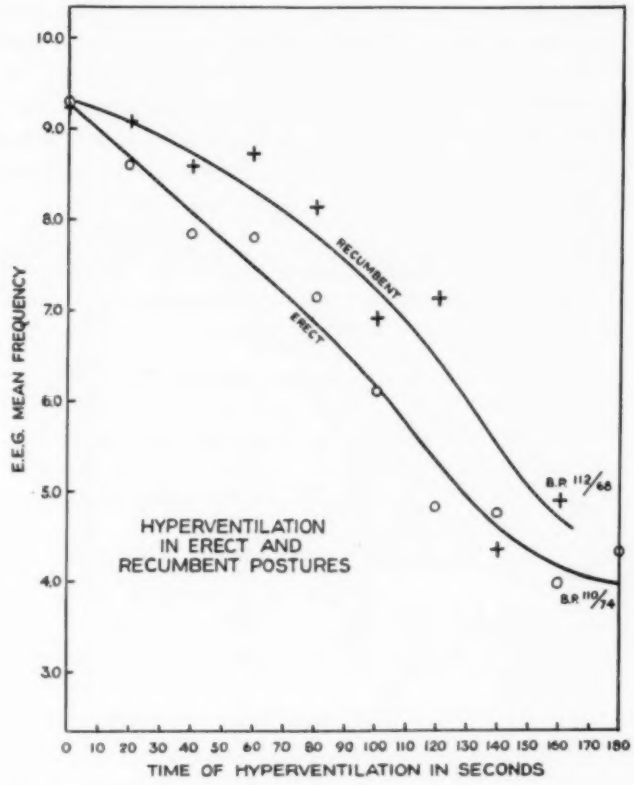

FIG. 4. Effect of hyperventilation on erect and recumbent position on E.E.G. mean frequency.

TABLE IV

Change in Electroencephalographic Mean Frequency, Pulse and Blood Pressure During Hyperventilation in the Recumbent and Erect Position

Subject	EEG (Mean Frequency) for 180 Sec. Period of Hyperventilation	Erect	Pulse (Maximum)	Erect	Blood Pressure (Minimum)	Erect	Blood Sugar mg. %
	Recumbent		Recumbent		Recumbent		
G. E. (1)	6.72	5.90	102	138	90/68	100/64	103
G. E. (2)	6.14	5.32	114	126	110/60	106/86	91
G. E. (3)	7.19	6.14	120	150	104/60	98/60	104
E. F. (1)	7.41	6.44	126	156	112/80	116/84	100
J. R. (1)	7.50	6.97	114	132	110/60	108/88	95
J. R. (2)	8.05	7.00	96	120	100/66	94/76	100
J. R. (3)	8.37	7.23	114	126	105/68	100/88	119
J. R. (4)	7.72	6.60	90	102	114/68	96/80	87
H. R. (1)	5.28	4.38	108	120	110/—	108/—	102
H. R. (2)	8.31	5.49	84	114	100/50	90/70	—

seen from table 5, there was a slight but significant increase in slowing during the period of activity of the drugs as compared to the control hyperventilation period.

In four experiments amyl nitrite was administered after the slow activity had become well established. In no instance was there any tendency for slow activity to diminish after the effect of the drug had made itself manifest

TABLE V

Effect of Nitroglycerine, Amyl Nitrite, and Nicotinic Acid on Electroencephalogram During Hyperventilation

Subject	Condition	EEG Mean Frequency									Blood Sugar mg. %	Comment
		Time of Hyperventilation in Seconds										
		Resting	30	50	70	90	110	130	150	170		
1	Control	8.8	8.5	8.2	8.3	5.0	5.1	4.2	4.3	3.8		
	Nitroglycerine 0.4 mg. (sublingual)	8.6	8.8	7.6	5.7	3.1	3.6	3.8	2.9	3.6		Flush Pounding in head
	Nitroglycerine 0.8 mg. (sublingual)	8.3	8.5	8.4	5.8	4.2	3.8	4.0	3.0	4.3	75	Flush Pounding in head
	Control	9.0	9.3	9.0	8.4	6.0	3.7	4.1	4.1	4.5	77	
	Amyl nitrite	9.3	9.5	8.0	5.3	4.8	3.0	4.8	4.3	3.4	84	Flush Head pounds
2	Control	9.6	9.5	9.1	8.6	8.8	8.3	6.7	7.0	7.0	68	
	Nitroglycerine 0.8 mg. (sublingual)	9.7	9.5	8.5	8.7	6.6	6.9	6.5	5.0	5.6	78	Flush Pounding in head Flush—pounding
	Amyl nitrite	9.8	8.8	8.7	8.5	8.3	8.0	5.6	7.1	4.5	77	in head. H.V. less adequate
3	Control	10.8	10.4	10.5	9.2	5.5	4.9	5.2	6.4	4.5	109	
	Nicotinic acid 100 mg. i.v.	11.0	10.0	9.8	8.7	5.6	5.0	4.5	4.1	4.8	102	Marked flush
	Control	10.7	9.5	9.5	8.6	4.5	4.8	6.2	5.1	4.9	99	
4	Control	10.3	10.0	10.4	7.4	5.6	4.7	4.0	3.1	4.6	95	
	Nicotinic acid 100 mg. i.v.	11.1	10.3	10.4	6.0	4.7	4.9	4.6	3.0	3.5	106	Marked flush
5	Control	10.9	11.2	10.7	10.8	10.1	10.6	9.9	10.4	9.8	148	
	Nicotinic acid 100 mg. i.v.	10.9	10.1	10.7	10.9	9.9	10.5	9.7	10.2	9.5	126	Severe flush Swelling of face

by the flushing of the face. In two subjects the pungent odor at first inhibited respiration for about 10 seconds and this was associated with some acceleration of the electroencephalogram, but this was transient, the slow activity resuming as soon as hyperventilation was resumed. It was difficult to establish whether there was increase in slow activity in this type of experiment.

Nicotinic acid (100 mg.) was administered intravenously to three subjects and hyperventilation begun when the flush had become well established.

There was no significant effect on the rate of slowing of the electroencephalogram.

Changes in symptoms could not be evaluated because of the side effect of the drugs themselves. In general reduction in consciousness seemed to be greater with amyl nitrite and nitroglycerine than with the control hyperventilation.

Of the three drugs used amyl nitrite probably produced the most marked increase in intracranial blood flow and nicotinic acid the least.[13] The magnitude of hyperventilation change in the electroencephalogram produced by these drugs, as compared to the effects of blood sugar and oxygen tension, is small and would suggest that vascular factors are not primary. Other studies support this suggestion.[4]

(h) *Effects of Calcium:* It is generally thought that the intravenous injection of calcium will prevent or diminish hyperventilation tetany, but the literature on this point is actually very unsatisfactory.[14] Although most investigators claim this to be so, we found only two cases reported in which susceptibility to tetany was recorded before and after the injection of calcium. O'Donovan found it effective in his case, while Schultzer and Lebel found it ineffective, in spite of raising the serum calcium from 10.5 mg. per cent to 12.0 mg. per cent.[14] There are no statements in the literature relevant to the effects of calcium on the disturbances in consciousness.

TABLE VI

Effect of Intravenous Calcium Chloride on Electroencephalogram During Hyperventilation

Subject	Conditions	EEG Mean Frequency									Blood Sugar mg. %	Comment
		Time of Hyperventilation in Seconds										
		Resting	30	50	70	90	110	130	150	170		
1	Control	10.7	9.5	9.5	8.6	4.5	4.8	6.2	5.1	4.9	99	
	$CaCl_2$ .75 gm. i.v.	10.6	10.1	9.6	9.3	8.7	5.3	6.6	6.5	4.3	113	Sl. Nausea
2	Control	10.6	10.8	9.6	9.8	8.7	8.2	7.8	7.2	7.4	94	
	$CaCl_2$ 1.0 gm. i.v.	10.8	10.5	10.4	10.3	10.4	10.4	9.8	8.9	9.4	131	
3	Control	10.7	10.7	10.2	8.9	7.0	5.8	5.3	5.9	3.2	95	
	$CaCl_2$ 1.0 mg. i.v.	10.8	10.7	10.3	8.8	8.1	6.7	3.4	3.8	3.1	106	

Three subjects hyperventilated before and again after receiving from 0.7 to 1.0 gm. calcium chloride intravenously (table 6). There was a slight tendency for less slowing after the calcium, but this could be adequately accounted for by the change in blood sugar. Two subjects noted less tingling during the hyperventilation after the calcium injection.

4. *Factors Influencing Tetany.*

Observations on tetany are incomplete because for the most part longer periods of hyperventilation than were used in these experiments are necessary to produce tetany. When loss of consciousness is marked and associated with involuntary cessation of hyperventilation tetany is unlikely to develop. Therefore the occurrence of tetany is less when slowing of the electroencephalogram is marked but it cannot be concluded that the factors which increase slow waves in the electroencephalogram also decrease tetany per se. On the other hand, when blood sugar or oxygen tension is raised sufficiently to prevent any electroencephalographic slowing, tetany will always develop if the hyperventilation is continued for a long enough period. It is obvious from our studies that there is no direct relationship between the electroencephalographic frequency changes and tetany. The two phenomena are more or less independent in development although under some circumstances they may be influenced in the same direction by the same factors, but not necessarily to the same degree.

Analysis of the subjective symptoms would seem to indicate that numbness, tingling, and stiffness of the extremities and perhaps tinnitus are peripheral and related to tetany, while the other symptoms are central and related to the reduction in level of consciousness. The former symptoms are more suggestive of peripheral nerve disturbance, the latter of cortical involvement.

5. *Syncope.*

Since fainting "spells," or "fits" are often the presenting complaint of patients with hyperventilation, it is well to analyze these phenomena in more detail. As has already been mentioned, most patients complain of symptoms related to reduced consciousness and express a fear of fainting, but true syncope, which implies both unconsciousness and falling, occurs relatively infrequently. We have never encountered it among normal subjects hyperventilating in the erect position on the tilt table, and as has already been noted, the fall in blood pressure in normal subjects hyperventilating in the erect position is not consistent or remarkable when postural adaptation is normal. Among patients at least four different mechanisms have been delineated. Some of these have already been discussed in other publications.[15]

(a) *Vasodepressor Syncope:* When anxiety is a prominent symptom vasodepressor syncope may occur concurrently with hyperventilation, where both represent physiological concomitants (circulatory and respiratory) of a vegetative neurosis. In such a case the electroencephalographic changes of hyperventilation and the circulatory changes of vasodepressor syncope are likely to occur simultaneously. While hyperventilating the patient is likely also to manifest pallor, sweating, weakness, falling blood pressure, eventually,

if erect, losing consciousness and falling. If recumbent the signs of vasodepressor syncope may be much less obvious.

Vasodepressor syncope may also occur as a delayed reaction in a hyperventilating patient, in whom the unpleasant and frightening symptoms induced by hyperventilation provoke increased anxiety which may then lead to vasodepressor syncope. In such a case the manifestations of vasodepressor syncope develop one to three minutes after hyperventilation may have been discontinued and after the E.E.G. has returned to normal. An example of such a case is illustrated in one of the papers referred to.[15]

(b) *Orthostatic Hypotension:* In patients with postural maladaptation, whose blood pressure falls upon assuming the erect posture, hyperventilation will usually accelerate this process. In such individuals fainting will occur early in hyperventilation, usually before any significant slowing of the E.E.G. has occurred, and will be accompanied by the usual signs and symptoms associated with orthostatic hypotension. An example of this is illustrated in the paper already referred to.[15a]

(c) *Hysterical Phenomena:* In patients in whom the hyperventilation is an hysterical symptom, a not uncommon sequel is hysterical syncope or an hysterical convulsion. In these patients the loss of consciousness may be brief or prolonged, may occur during or after hyperventilation, may occur in any posture, is sometimes associated with bizarre movements, and is not accompanied by any significant slowing of the E.E.G.[16] If slowing of the E.E.G. does occur during hyperventilation the loss of consciousness is likely to persist for variable periods after the E.E.G. has come back to normal. Nor are there any changes in skin color, pulse, or blood pressure other than those which are usually seen during hyperventilation and which disappear when hyperventilation stops even though unconsciousness may persist. Psychiatric investigation of these patients always reveals the characteristic dynamics of hysteria and it is usually relatively easy to reproduce the syndrome in an experimental setting; merely examining the patient on the tilt table, with appropriate suggestions, is often sufficient to initiate involuntary hyperventilation and the characteristic train of symptoms. Unless unconsciousness persists for some time after hyperventilation has ceased, however, an E.E.G. is necessary to establish that the loss of consciousness is not the result of the acapnia alone.

(d) *Cerebral Type:* This type is not based on experimental study but is deduced from clinical observation. We occasionally see patients who describe sensations of impending loss of consciousness lasting for some minutes which occur during hyperventilation. They finally fall unconscious. While these may be hysterical in some cases the reduction in consciousness may be so marked that the patient cannot maintain the erect position and falls. This occurs rarely because breathing usually stops reflexly before unconsciousness comes on so that while the person is continually on the verge of fainting he doesn't actually do so.

Discussion

These studies clearly demonstrate that there are two components to the symptomatology provoked by hyperventilation. Reduction in consciousness, with its associated symptoms of giddiness, faintness, lightheadedness, fullness in the head, blurring of vision, etc., appears to be correlated with certain prominent changes in the electrical activity of the cortex. These changes in electroencephalographic activity can be modified by changes in blood sugar, oxygen tension of inspired air, rate of hyperventilation, posture, and certain cerebral vasodilators. In the absence of E.E.G. slowing of a certain magnitude consciousness is unchanged. Tetany, on the other hand, with its associated symptoms of muscle cramping and stiffness, hyperirritability of muscles, carpo-pedal spasm, etc., appears not to be associated with the presence or absence of changes in the electrical activity of the cortex. Numbness and tingling are also more prominent when the E.E.G. is unchanged. This suggests that these symptoms are essentially peripheral in origin and supports similar conclusions reached by Harvey and Lilienthal.[17] Whether the factors that influenced the electrical activity of the cortex have any influence on the peripheral phenomena, and if so, in what direction, was not established with certainty in this study because of the relatively short periods of hyperventilation used in most of the experiments and because of the reduction in consciousness which precluded evaluation of objective symptoms. We have observed many instances, not included in this series, in which tetany developed at high altitude, during hyperventilation with 100 per cent oxygen, at varying blood sugars, and in various postures. While more careful observations may reveal some quantitative differences under these varying conditions, it is still clear that they are minor as compared to the effects on consciousness.

Nor did our studies clarify the relationship between the numbness and tingling and the tetany. Numbness and tingling is one of the earliest symptoms to appear during hyperventilation and is usually most marked when consciousness is maintained. Because of the subjective nature of this manifestation, it proved difficult to study since the variations in consciousness prevented accurate reporting on the subjects. While it is conceivable that it is central in origin, this seems unlikely. Clinically this numbness and tingling is more suggestive of peripheral nerve involvement and resembles the symptoms seen during compression of a nerve. Indeed, the presence of a blood pressure cuff on one arm during hyperventilation may lead to earlier and more severe symptoms in that extremity. Tetany, as all have emphasized, appears after much longer periods of hyperventilation and is much less frequent. It is suggested that the numbness and tingling represents a disturbance of the sensory components of the peripheral nerve while tetany represents a disturbance in motor function. Change in response of the sensory end organ and of the muscle must also be considered. Such discrepancy between peripheral sensory and motor function is, of course, well known.

The literature has tended to emphasize tetany as the chief manifestation of hyperventilation. It is our impression, derived both from clinical and from experimental observations, that the reduction in consciousness develops much earlier than does tetany and is much more disturbing to the patient. Indeed, we have seen relatively few patients who have described tetanic symptoms as the presenting complaint. A sense of reduced awareness is almost invariably an extremely frightening experience.

The ease with which a reduction in consciousness may be produced in most people by hyperventilation offers a convenient clinical tool for the study and examination of psychiatric patients.[18] By this means one is often able to effect in resistant patients the release of more inhibited or less well integrated behavior which may be of diagnostic and sometimes therapeutic value. It is particularly useful in hysterical patients in whom hysterical manisfestations may be induced by the procedure or in whom the reduction in consciousness renders the patient more susceptible to suggestion, allowing for the possibility of relief of hysterical symptoms. In amnesic or uncommunicative patients contact may sometimes be established by this device, which may be compared to the use of pentothal.

It is a common misconception that hyperventilation may provoke a major epileptic seizure. While petit mal attacks are readily provoked by hyperventilation, in our experience true grand mal attacks have never been so provoked. All the "attacks" which we have seen provoked during hyperventilation have subsequently proved to be hysterical.

The implication of these observations to problems of aviation medicine deserves some comment. Increased ventilation is a reflex reaction to anoxia leading to increased alveolar pO_2 (due to reduction in alveolar pCO_2) and to a greater uptake of oxygen in the lungs due to the alteration in the dissociation of oxygen from hemoglobin because of alkalosis (the Bohr effect). As long as in a normal person this is controlled by purely reflex and physiologic factors, it seems likely that the magnitude of hyperventilation will tend to remain within zones in which the advantageous effects outweigh the disadvantageous effects. However, with the introduction of various intermittent pressure breathing devices hyperventilation is produced which is dependent on other factors, including the construction of the pressure breathing device. It soon became apparent that a considerable part of the rise in arterial oxygen saturation during pressure breathing is the result of hyperventilation and not of the increased pressure, and this led to the suggestion that the voluntary hyperventilation itself may be used as a means of gaining altitude.[19] Our studies indicate that both these procedures may be hazardous. The induction of disturbances of consciousness is subtle and it may be easily overlooked unless specifically sought for. Further, not only is there considerable variation among individuals as to the ease with which consciousness is disturbed by acapnia, but there are many variables in each individual that would be difficult to control under flight conditions. Since it is almost

impossible to control ventilation voluntarily by mechanical devices so that only an optimum degree of reduction in pCO_2 is produced, the danger of acapnia is ever present. Otis, Rahn, Epstein and Fenn [20] using the Hecht Visual Contrast Discrimination Test and a hand steadiness test have confirmed our observations indicating that the effects of anoxia and acapnia are additive in most zones.

Summary

1. Hyperventilation may occur as a response to certain intense emotional experiences in normal people, as a vegetative neurotic symptom, as an hysterical symptom, as a symptom of diffuse encephalopathy and certain drugs, and as a response to anoxia.

2. The symptoms may be divided into those related to reduction in consciousness and those related to tetany.

3. Reduction in consciousness is found to correlate well with the degree of slowing of the electroencephalogram and is usually marked when the mean frequency is reduced below 5.0 per second.

4. Slowing of E.E.G. frequency during hyperventilation is more marked with:

(*a*) rapid reduction in arterial CO_2 content
(*b*) low blood sugar
(*c*) low oxygen tension of inspired air
(*d*) the erect posture
(*e*) amyl nitrite and nitroglycerine.

Conversely, high blood sugar, high oxygen tension, and the recumbent posture diminish E.E.G. slowing.

5. Intravenous injection of calcium chloride and nicotinic acid has no effect on E.E.G. during hyperventilation.

6. Tetany is unrelated to changes in E.E.G. and occurs with longer periods of hyperventilation. The numbness and tingling probably are also peripheral in origin.

7. Actual syncope is unusual during hyperventilation. Four different mechanisms have been observed:

(*a*) concurrent or delayed vasodepressor syncope
(*b*) accentuation of already present orthostatic hypotension
(*c*) hysterical syncope
(*d*) central type.

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A SURVEY OF RECENT DEVELOPMENTS CONCERNING THE CONCEPTS OF CORONARY DISEASE AND ITS MANAGEMENT *

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Coronary disease is one of the most important diseases afflicting mankind. As the medical profession has reduced infantile mortality, improved sanitation, developed antibiotics and learned to deal with epidemic diseases, there has been a constant shift towards an increase in the frequency of degenerative diseases, like hypertension, arteriosclerosis, cancer, and their sequelae. Arteriosclerosis is thus becoming an ever growing problem and it will continue to grow in importance as the population becomes older. Arteriosclerosis is not a matter of aging, though it is more common in the elderly. It is a disease which affects not only old people, but also middle aged people and even young people. The concept that arteriosclerosis is a disease process and not just aging should ultimately prove fruitful in advancing our knowledge.

Arteriosclerosis can cause disease in all parts of the body, but the statistically important forms, as far as serious consequences are concerned, are nephrosclerosis, cerebral arteriosclerosis and coronary arteriosclerosis. It is fair to say that one out of every two persons in this audience will, unless something specific is found in the interim, succumb to coronary disease. Not only is this true of the medical profession but it is likewise true of other professions and of the executives, the people upon whose intelligence the welfare of this country depends to a large extent. We do not know why it is that the male suffers more ill effects from arteriosclerosis than does the female, nor why the "brain truster" in the broadest sense withstands this disease so much less than the average male population. Some day the answers will come. Apparently one of the prices paid by an individual for becoming a professional or executive type is that his chances of succumbing to coronary disease are greatly enhanced.

The fundamental cause of arteriosclerosis is poorly understood and the specific methods available to prevent or even to retard its development are practically nonexistent. This is one of the most important basic problems in medicine. The experimental work in the field of arteriosclerosis is clear in showing that cholesterol is involved in its development and that the feeding of cholesterol with the accompanying hypercholesterolemia induces atherosclerosis in the herbivorous rabbit and the omnivorous chicken, and that, when supplemented by thiouracil, it apparently can also induce this

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lesion in the dog. Experimental evidence also supports the idea that strain upon the circulation facilitates its development. It appears also that thyroid secretion and potassium iodide tend to retard it, while hypothyroidism tends to favor its development. Other factors involved in the process of experimental atherosclerosis are still controversial. In the present state of our knowledge it is not yet justified to advocate a cholesterol-poor diet in man in the hope of retarding atherosclerosis because there is reason to believe that endogenous cholesterol produced even on a cholesterol-poor diet may still lead to atherosclerosis. Recent experience in animals has suggested the possibility that macromolecular substances lead to blood vessel plaques and it may be that cholesterol operates as a macromolecular substance. Some inconclusive experiences suggest that ischemia or anoxemia of the vascular wall, which is normally richly supplied by vasa vasorum, contributes to the development of atherosclerosis. These are the problems for the future. For the present these concepts cannot yet be employed in the clinical handling of arteriosclerosis.

When we speak of coronary disease we speak statistically primarily of coronary atherosclerosis and its sequelae. However, the coronary blood vessels are subject to other diseases, such as periarteritis nodosa, thromboangiitis obliterans and other less clearly defined vascular diseases. Emboli, usually from preëxisting thrombi but also of material from valve vegetations, especially in subacute bacterial endocarditis, also lodge in the coronary arteries. Rheumatic coronary endarteritis is said to occur. Syphilitic closure of the coronary ostia is common. Invasion of the coronary vessels by cancerous growth and traumatic damage to the coronary vessels are observed. I mention these other causes simply to reëmphasize that atherosclerosis, while the most important single cause of coronary disease, is not the sole cause.

Coronary sclerosis leads to ill effects by handicapping the adjustments of the coronary vessels to the needs of the heart for varying amounts of blood flow. The rigidity of these vessels which is an accompaniment of coronary sclerosis makes them less distensible and hence more poorly adapted for wide variation of blood flow such as is required to meet the ordinary and extraordinary demands put upon the heart. While coronary sclerosis tends to develop in discrete locations, rather than diffusely, this interference with distensibility is still a serious consequence. Sclerosis of a coronary vessel also leads to narrowing of the lumen and thus interferes with the blood flow to the region which it supplies.

There are compensatory blood channels, namely the intercoronary communications, arteriovenous anastomoses, Thebesian vessels and extra-cardiac collaterals, which enlarge and take over the supply of blood to the region whose coronary artery is occluded or narrowed. The adequacy of this auxiliary blood supply depends most of all upon the rapidity of the narrowing of the coronary arteries. Age is also of some importance because the

coronary arteries are more nearly end arteries functionally in the young than in the old in whom these auxiliary channels have had time to develop. Clinically this is demonstrated by the fact that closure of a single coronary vessel is apt to lead to infarction in a young individual whereas in an older person closure of more than one vessel supplying a region is ordinarily required before infarction occurs. The rôle of the Thebesian vessels is shown by the fact that infarction of the lateral wall of the right ventricle occurs only once in every 40 cases. This is so because it has been demonstrated that 90 to 95 per cent of the Thebesian vessels open into the right heart. In the left heart where infarcts are more prevalent the Thebesian drainage constitutes at most 5 to 10 per cent. Personally, I believe that the infarcts of the lateral wall of the right ventricle arise by virtue of the endocardial thromboses which plug up the openings of the Thebesian vessels. The rôle of the extra-cardiac collaterals is clearly revealed by the occasional finding at necropsy of almost complete syphilitic closure of both coronary ostia with little or no disability on the part of the patient for many years until a few months before the rapid downward course leading to death. Thus, in understanding the ill effects of coronary disease account must be taken not only of the coronary abnormalities themselves but also of the manner and completeness of the compensatory secondary circulation which can take over the task of feeding the impoverished areas of the heart.

An examination of the architecture of the coronary vessels at necropsy as ordinarily performed by the traditional pathologist fails to reveal the nature of collateral circulation. It also fails to determine the state of the smaller arteries and the arterioles. The presence of a plaque need not indicate narrowing of the lumen since in several instances experimental distention of the involved coronary artery with a pressure of the order existing in life has revealed aneurysmal dilatation at this point. The practice of injecting the coronary system in necropsy examinations should be more widespread. For these and other reasons, examination of the coronary vessels at necropsy often fails to provide sufficient evidence from which the clinical course of the patient can be reconstructed. This is not surprising since an examination of the water and sewage system of a municipality confined to an examination of the pipes is inadequate to reconstruct the ability of the system to provide water and to remove sewage. It is obvious that the pumps and the other factors involved must be examined in arriving at a complete analysis. This is true also of the coronary system. Other factors besides the architecture of the coronary vessels are involved in determining the adequacy of coronary flow. A dynamic viewpoint which takes into account all the factors must be employed therefore in analyzing coronary disease for clinical purposes. The functional state of the coronary vessels and the dynamics of the coronary flow must be evaluated. It is for this reason that the term coronary insufficiency to express an inadequate coronary flow has been created and gained wide vogue recently. This dynamic or physio-

logical concept serves a useful purpose in that it permits the clinician to judge whether the coronary system is able to nourish the heart adequately.

Coronary insufficiency from the clinical standpoint involves two factors. One is the absolute rate of coronary flow, the other is the need, per unit of time, for coronary blood flow to maintain the heart in the status quo. Even in the normal heart excessive exertion may so increase the need for coronary blood flow that the compensatory mechanisms available to increase the normal coronary circulation may fail and coronary insufficiency may ensue. Coronary insufficiency therefore is really to be expressed in terms of relative insufficiency. It arises whenever the coronary blood flow can not keep up with the needs for it. This may be due either to an increase in the need or to a reduction in the supply.

Coronary insufficiency may be focal, involving only a portion of the heart, or it may be generalized, involving the entire heart. Focal coronary insufficiency is more apt to lead to pain of cardiac origin and to confluent myocardial infarction while generalized coronary insufficiency is more apt to lead to chronic or acute heart failure. Obviously exceptions occur.

Coronary insufficiency can be subdivided also according to the time of its duration. Thus, transitory coronary insufficiency, which is the cause of anginal attacks, acute heart failure, paroxysmal dyspnea and acute pulmonary edema, lasts for a matter of minutes or an hour or so. It may be terminal, of course, ordinarily by leading to ectopic rhythms arising in the ischemic area which terminate in ventricular fibrillation.

Coronary insufficiency may be more protracted and lead to myocardial infarction.

Coronary insufficiency may be chronic. Many patients with a healed myocardial infarct may go into this chronic state. Two varieties of chronic coronary insufficiency exist. The first is benign. The symptoms and signs of the coronary insufficiency progress very little over months and years apparently because the compensatory collateral circulation can make up for the primary defects. The second variety is more malignant. Here the primary defect progresses inexorably faster than the compensatory mechanisms can keep up with it, with the result that the signs and symptoms progress continuously, and sometimes at an accelerating rate, until death. Of course, the transitory and the protracted forms of coronary insufficiency are often superimposed upon the chronic coronary insufficiency and may be the terminal event.

Coronary insufficiency, therefore, is primarily a chronic disease of benign or malignant character. More attention needs to be paid to this aspect of coronary disease despite the lure to concentrate on the more dramatic episodes of transitory coronary insufficiency and acute myocardial infarction. We need to consider coronary disease as a long term problem and to concern ourselves with this aspect of it more than we have in the past. Of course, this does not mean that we should pay less attention to the acute varieties.

In order that we may understand the rationale of prognosis and management of coronary insufficiency we must be aware (1) of the natural history of coronary disease and (2) of the factors involved in the control of the coronary circulation.

In considering the control of the coronary circulation too much attention has been directed in the past to the effects of change in caliber of the coronary vessels due to its musculature and not enough to the other factors involved. Coronary insufficiency, I believe, occurs more often by virtue of disturbances of the dynamics of coronary flow and to anatomic narrowing and obstruction of the coronary lumina than to coronary vasoconstriction or spasm. In fact, I would hazard the guess that coronary spasm is a rare occurrence and coronary vasoconstriction is relatively infrequent. This is not to be taken to mean that coronary vasodilator drugs are ineffective, but their rôle is to supplement coronary flow rather than to relieve vasoconstriction.

In considering the control of the coronary flow, it must first be pointed out that the coronary vessels are to a large extent enclosed within the walls of the heart chambers which undergo changes in tension during the heart cycle. In the case of the right ventricle, the cyclic change is of the order of 50 mm. of mercury, and in the case of the left ventricle it is of the order of 180 mm. of mercury. As these pressures rise in systole they exert a squeeze upon the coronary vessels which tends to narrow them and cause a systolic retardation in flow. Actually the situation is more complex. Thus it has been shown that the subendocardial layers of the ventricles are the only ones in which this magnitude of squeeze takes place. In the subepicardial regions the pressure actually remains around zero during the heart cycle. In short, the squeeze due to the systole of the ventricles applies only to subendocardial layers and lessens across the thickness of the ventricular wall until at the epicardium it is practically absent. This is the reason that focal necrosis, the anatomical sign, of transitory coronary insufficiency, is more prevalent beneath the endocardium.

Far more important is the fact that the coronary blood flow is dependent upon the fluctuations in pressure at the root of the aorta which is the driving force for the coronary flow. Since the aortic pressure is higher in systole, it would appear that, except only in the subendocardial layers of the left ventricle, there is normally a systolic accentuation of coronary flow. Furthermore, it is possible that under abnormal conditions, such as strain of the right heart, the systolic rise in wall tension in the right heart may be greater than the systolic rise in aortic pressure, leading to a systolic slowing of the coronary circulation in this part of the heart.

Since 90 to 95 per cent of the coronary drainage is into the right heart it follows that acute engorgement of the right heart such as occurs in recent pulmonary embolism and acute congestive right heart failure will impede coronary flow and lead per se to coronary insufficiency. This is particularly striking since at the same time the need for coronary blood flow in the right

heart is increased because the work of the right heart increases. A similar effect though less striking may occur in chronic congestive right heart failure.

Recently we have demonstrated in animal experiments that the coronary flow is a direct function of the cardiac output. The blood propelled by the left ventricle is distributed between the coronary vessels and the rest of the systemic circulation and both of these tend to fluctuate in the same direction as the output of the heart. This is an important mechanical regulation of coronary flow according to the need for it. This adjustment of coronary flow to cardiac output may occur with little or no rise in blood pressure. The clinician should be aware of this, since otherwise he would be hard put to explain how the coronary flow increases in cases of exercise, anemia and hyperthyroidism in which the blood pressure may be changed very little, if at all. Arteriosclerosis of the coronary vessels with their resulting rigidity permits the development of coronary insufficiency when the heart pumps more blood per minute, since the rigidity of the coronary vessels prevents the beautiful mechanical adaptation of coronary flow to cardiac output present in uninvolved coronary vessels.

Another thing that is lost sight of is that the coronary circuit is only one of many in parallel in the systemic circulation. Hence, vasodilatation or vasoconstriction of other paths of the systemic circulation, notably the splanchnic area, will divert some of the blood pumped out by the left ventricle away from or into the coronary circulation. Ordinarily this is accompanied by a blood pressure fall or rise, but in animal experiments we have seen this occur without significant change in blood pressure. We attribute this lack of blood pressure change to the fact that the diverted blood mechanically alters the caliber of the coronary bed so that the resistance to flow over the coronary circuit is sometimes affected to the same extent as, but in the opposite direction to, that in the other systemic circulatory beds. It is easy to conceive of mild adjustments in the caliber of the extracoronary systemic beds occurring clinically and resulting in diversion of blood to or away from the coronary circulation without a noticeable change in blood pressure. In fact, some of the drugs which are employed to dilate the coronary vessels may defeat the purpose for which they are used by virtue of their having a greater dilatory effect on other systemic circuits; and this may happen without their appreciably changing the blood pressure.

The caliber of the coronary vessels can be changed by vasomotor influences. Our own experience, contrary to those of others, has shown that the vagi are coronary dilators and not coronary constrictors. This is a cholinergic effect since the vagal coronary dilation is prevented by the exhibition of atropine. The sympathetic nerves, when their effect on cardiac work and metabolism is eliminated, cause both a vasodilation and a vasoconstriction of the coronary circuit. The sympathetic vasoconstriction is the more powerful and is adrenergic since it can be abolished by ergotamine

and the dioxane derivative, F933. These nervous influences are constantly active, as we have shown, but they are not powerful. They are as weak as the influence of nerves in controlling cerebral and pulmonary blood vessel caliber. Vasoconstriction of neurogenic origin, on this basis, must be sympathetic in nature and not vagal. Our own experiments have failed to show a vagal vasoconstriction of the coronary vessels and are opposed to the so-called vagal pulmono-coronary vasoconstriction reflex. Atropine if it has any benefits in myocardial infarction and in pulmonary embolism must operate in other ways than the supposed abolition of vagal coronary vasoconstriction.

When we eliminated all these extraneous effects in our animal experiments, we found that most drugs are coronary dilators. Among the most powerful are the nitrites and papaverine. The xanthines are much weaker and would appear to be ineffective when given by mouth. Acetylcholine and mecholyl are coronary dilators and their effect is abolished by atropine. Morphine, quinidine, calcium and sodium are coronary dilators and so is potassium in small doses. Potassium in large doses, however, is a powerful vasoconstrictor, leading to real coronary spasm. Pitressin, too is a powerful coronary vasoconstrictor, and so is foreign species blood. Adrenalin is a strong coronary dilator. Its ineffectiveness clinically as a coronary dilator is due to the fact that its side actions lead to an increased need for coronary blood flow far in excess of its dilator effect, with the net result that a relative coronary insufficiency develops. This illustrates that the determination of a vasodilating action of a drug does not per se indicate its utility in coronary insufficiency. Obviously adrenalin is not to be used as a coronary dilator clinically. In fact, it has been used as a method of bringing about coronary insufficiency as a clinical test for coronary disease. This illustrates that data obtained from animal experimentation can not be taken as applicable in clinical disease without first checking by clinical tests. Animal experimentation tells what can happen under controlled conditions but does not necessarily tell what does happen in the diseased patient. The latter belongs to the discipline of clinical research.

The story of the control of the coronary circulation would not be complete without mention of the final adjusting mechanism which depends upon unknown vasodilator substances which appear whenever relative ischemia or anoxemia of the heart occurs. It has been clearly shown that a lessening of the oxygen content of the arterial blood leads to coronary vasodilation and we have shown that temporary occlusion of a coronary vessel is followed, as in the case of other systemic circuits, by a powerful reactive hyperemia. This implies that there is a final adjusting mechanism which regulates the caliber of the coronary vessel to need. The development of anoxemia or ischemia, which ensues when compensatory mechanisms fail, tends to produce vasodilator substances which adapt the coronary flow to the needs at the moment. Obviously when the maladjustment is great even this final adjustment fails and relative coronary insufficiency results.

My purpose in this long digression on the control of the coronary circulation has been to bring you up to date on the complexity of the factors involved in regulating the blood supply to the heart and to make you ask yourself critically whether many of the glib explanations prevalent in current clinical thinking are really true or not. The first step in the rational approach to therapy and management of coronary disease is to remove taboos and fads which tend to creep in to any field of medicine as a result of its authoritative development. It is for a similar reason that I would like to discuss the mechanism of cardiac pain.

Of course, you know that not all chest pain is cardiac in origin. Many processes tend to imitate angina pectoris and these must first be excluded in every case where any doubt exists. It is notorious that the symptomatology of coronary disease is elusive. That is one of the reasons why electrocardiography has lately gained such vogue, but even here there is a tendency to read too much into the electrocardiogram and I would not be rash in stating that all of us have erroneously diagnosed many cases of chest pain as of cardiac origin. The interpretation of the electrocardiogram is subjective and as prone to errors as any other clinical method of diagnosis. We all know that a normal electrocardiogram does not necessarily exclude coronary disease. It is becoming clearer also that many other diseases can lead to electrocardiographic distortions which are imitative of coronary patterns. A need has developed for some tests to measure the adequacy of the coronary circulation.

Two such tests are now in vogue. One is the anoxemia test which I consider too hazardous for widespread use, even though its advocates point out that the administration of oxygen will quickly alleviate its untoward effects. The other is the exercise tolerance test with which we have recently gained some experience. This test depends upon quantitative exercise with the Master stairs and the observation of the electrocardiographic changes induced by it immediately after exercise and over the next 10 minutes. This test must be performed carefully, it is to be used only when the electrocardiogram is normal or at most shows non-specific abnormalities. It should be carried out only by a trained physician who has been instructed in its methodology. It should be stopped whenever pain, fatigue, or shortness of breath begin to appear. It has been the experience of those who have used this test that it will bring out positive evidence of coronary disease in a number of occult or otherwise doubtful instances. In this way it is of value in the clinical assay of a case suspected of chronic coronary insufficiency. Unfortunately the positive results occur in only a small percentage of cases so that a negative test does not exclude coronary insufficiency. In our hands, false positive tests have not as yet occurred. The changes we believe should not be dealt with quantitatively, but the interpretation should depend upon changes in the final segment, the S–T–T complex, similar to those encountered during a spontaneous attack of transitory coronary insufficiency.

Time does not permit me to analyze these electrocardiographic changes in detail. Nor is there time to consider the routine electrocardiogram of coronary insufficiency.

Angina pectoris implies the appearance of pain. The physiology of sensation is therefore applicable. This involves the determination of the pain stimulus, the location of the pain endings in the heart, the paths pursued by the pain fibers, the psycho-physiology of pain appreciation and the general physiology of referred pain.

The evidence is fairly complete that the pain substance giving rise to cardiac pain is a diffusible material which can pass in and out the blood stream readily. It is non-volatile in the sense that it can pass unchanged through the lung circulation. It is formed during ischemia of heart muscle and is destroyed in the presence of an adequate blood supply. It is not clear whether it is an acid metabolite like lactic acid, phosphoric acid, pyruvic acid or succinic acid, or is a non-acid metabolite like histamine, phosphocreatine, adenosine or potassium. It appears that it can be manufactured by ischemic skeletal muscle as well as by heart muscle and this is important since the skeletal musculature constitutes half the body mass. Because the stimulation involves end organs, the substance must accumulate in quantities above a threshold in order to stimulate the pain endings. This means that in the absence of pain, the pain-producing material need not be absent but may be at any level below the threshold. Obviously, therefore, the amount of further accumulation of pain-producing material may be variable since at one extreme there may be none of this material present beforehand and, at the other extreme, it may have already accumulated to just below the threshold level.

The pain endings in the heart, aside from those in the parietal pericardium, appear to be located only in and around the coronary vessels. It is there that the pain-producing substance must accumulate. Experience has shown that the epicardium, endocardium and myocardium are free of pain endings. The pain fibers are located in the adventitia of the coronary vessels and travel up to form a plexus around the mouths of the coronary arteries. There they are joined by pain fibers coming from the root of the aorta and others from the great vessels as well as those from the parietal pericardium. The pain fibers join the cardiac plexuses in the mediastinum and travel to the spinal cord and medulla via the sympathetic chain and the vagi, and eventually reach that part of the cortex where the sensorium is located. Pain fibers and other fibers from somatic regions of the same segmental area join these visceral pain fibers at various levels so that at the sensorium there is a final common terminal for these visceral and more commonly experienced somatic sensations.

The pain endings of the heart, like other end organs of sensation, may vary in the level of their threshold, that is they may require more or less of the pain producing substance to stimulate them under different circum-

stances. This variability may result from coronary disease. Mild degrees of ischemia may make the end organs more sensitive; greater degrees may dull them and even destroy them. Disease may also affect the pain pathways of the heart. Since arteriosclerosis involves the vasa vasorum nourishing the adventitia of the coronary vessels it is possible that the disease process may irritate these fibers and so lead to stimuli engendered at these irritable foci rather than at the nerve endings themselves. More advanced disease may inhibit the transmission of nerve impulses over these pain fibers and may even destroy them. This is another variable in the development of pain sensations from the heart.

People vary greatly in their ability to appreciate painful stimuli. There are hypo- and hyper-sensitive persons as far as pain is concerned. This too introduces an element of variability. It is quite likely that conditioning plays an important rôle in making the pain sensation obtained more readily appreciated. It would appear that the more often painful stimuli occur, the more often angina will develop, that is, the more readily pain can be appreciated. It follows, therefore, that any procedure that will keep a patient free from anginal attacks will, as it were, uncondition him and make it harder for anginal pain to recur.

One of the peculiarities which heart pain shares with all referred pain is that it is referred to somatic areas from which the person is more accustomed to perceive sensation than from the heart. This you are all aware of by virtue of the classical and less common somatic distribution of pain of cardiac origin. It would take us too far afield to enter into the matter of referred pain. However, I wish to stress that irritation in the aorta, in other visceral organs and in somatic areas may make anginal pain appear more easily. Impulses coming from somatic areas may summate in the final common terminal with those from the heart and so require less pain stimulation of the heart to give rise to the sensation of cardiac pain. We have been able to show that exercising the left hand in patients susceptible to angina, while the blood supply to the hand is cut off by a blood pressure cuff, can often induce a typical minor anginal syndrome. Apparently the painful stimulation from the hand summates with the sub-threshold stimulation of the heart so that the two together can be appreciated by the sensorium as pain.

These few remarks on the pathogenesis of pain should orient the clinician in his interpretation of the meaning of this sensation. He should appreciate that just because cardiac pain is a threshold phenomenon, the appearance of pain will come on and wax briskly since the heart is constantly beating. This does not imply that angina is due to coronary spasm. Any circumstance which causes a rapid accumulation of pain-producing substances will lead suddenly to the appearance of pain. This concept of angina pectoris will help the clinician to explain the otherwise inexplicable lack of relationship of anginal pain to effort, why sometimes little effort leads to pain and

at other times in the same patient much greater effort does not. It is the state of the nervous system and the rate of accumulation and disposal of the pain-producing material that accounts for this variability.

There is one other matter I would like to discuss briefly and that is the difference in effect on the heart of a short and prolonged period of ischemia. The difference in effect between a transitory and a protracted period of coronary insufficiency is a matter of degree and a matter of reversibility. For example, it can be shown that when a coronary artery is occluded the region supplied no longer contracts but bulges during systole. If the occlusion is released at the end of a minute or so the power to contract once again develops, but if the occlusion is kept up for several minutes the change is irreversible. Similarly, on occluding a coronary artery the region supplied will show a decline in the content of glycogen, phosphocreatine and other chemical precursors of contraction. At the same time phosphoric acid, lactic acid, pyruvic acid and succinic acid increase. If the coronary artery is released at the end of a minute or so these changes are reversed but if the occlusion is released after five or more minutes the change becomes irreversible. A similar difference between a minute and several minutes of occlusion can be demonstrated for the development of acidity in the ischemic area. It has further been demonstrated that if animals are taken and the coronary arteries temporarily occluded for five minutes and then the chest closed and the pneumothorax relieved, that a series of electrocardiographic changes develop such as are encountered following myocardial infarction. This is true also if the experiment is repeated in other dogs but the occlusion kept on for 15 or more minutes. However, when these animals are sacrificed later it is found that the shorter occlusion had not led to histologically recognizable infarction while the latter had. These experiences show that occlusion operates at first in a reversible fashion and only when it is prolonged do the effects become irreversible and capable of histological demonstration. Thus, histo-biochemical changes precede histo-anatomical ones. It is fair to state that the local effects of ischemia are related to the product of the severity and the duration of the ischemia.

I am sure that by this time you have begun to ask yourselves how these fundamental problems help in the diagnosis, prognosis and management of coronary disease. As for diagnosis, what I have said shows why history alone may often be misleading, why there is need for objective tests. Much remains to be done in this field, but with the consideration and exclusion of other causes of these symptoms, with the aid of properly analyzed electrocardiograms, and with such procedures as the exercise test, the diagnosis of coronary disease may become more precise.

As to prognosis, it is obvious that the clinician must become familiar with the average development in coronary disease. He must recognize that about one-fifth of the cases of recent myocardial infarction die during their hospital stay; that the average expectancy of life, following an infarct is five

years, but that the scatter is quite large. We have seen cases who have lived very comfortably for over 20 years following an infarction. We are all aware of the fact that the factors which determine the prognosis in recent myocardial infarction and in other forms of coronary disease are still too poorly understood for us to be able to prognosticate accurately in a given patient. It is true that those people who develop a marked drop in blood pressure or go into shock have a poor prognosis. It is true that the development of congestive heart failure carries with it a serious outlook. It is true that the presence of diabetes adds to the gravity of the outlook. Nevertheless we do not know how to prognosticate precisely how long a given patient with coronary disease will live. It is therefore unwise to give a poor prognosis. Too many patients with coronary disease are frightened unnecessarily by their physicians and many who otherwise might lead a useful and happy existence are made miserable and useless by an unjustified poor prognosis.

Of course, the patient should have his affairs in order, should be moderate in his undertakings, should learn how to play as well as how to slow up in his work, how to cut down and avoid peak loads, how to develop a carefree attitude, how to keep his weight down to normal—in short, he should learn how to live. But to take him away entirely from his life's occupation, to let him live on disability insurance, is in most cases unnecessary and even harmful. Ninety-five per cent of all coronary fatalities appear to occur without precipitating cause, many occur during bed rest or sleep. In our present state of knowledge we know too little of how to prevent the further progress of atherosclerosis and its sequelae to warrant prohibitions.

When coronary disease was first recognized, myocardial infarction was a necropsy diagnosis so that the impression arose that it was inevitably fatal. As our knowledge grew and it became clinically recognizable, infarction became less ominous. Today we know that many people have had infarcts without any symptoms, without any special medical care and the knowledge of this was written in their hearts and revealed at necropsy some time later when they died of some other circumstance or of a new infarction. I have seen the hearts of some of these people who have worked in hospitals or in close association with doctors and who had their infarction without enough symptoms to warrant their consulting the readily accessible physicians. I have seen this too in the hearts of doctors. You are all aware of the fact that before we became coronary conscious, many people had indigestion as a sole manifestation of their coronary episode. In short, coronary disease is more prevalent than we realized and even infarction is statistically more benign than we appreciated.

I would like to emphasize that I consider myocardial infarction a self-limited disease, a process which by the time the clinician sees the case is ordinarily already a matter of convalescence, that four out of five patients will survive the episode, and that most of them will have little if any handicap.

Some of course will develop chronic coronary insufficiency, but others will be completely restored and have, at most, only the psychological fear that all lay people and too many physicians attach to coronary episodes. I think all of us should practice the psychology of hope. There has been too much of the psychology of fear.

As already hinted the primary management problem in coronary disease is to deal with chronic coronary insufficiency. This is a problem involving more than medication. It is a problem in which the physician has to survey with his patient the entire mode of his existence and to try to create a proper philosophy of living. This should be adapted to the temperament of the patient. The fearful one will have to be reassured, the domineering one will have to be taken down a peg or so. It is in this field that a sympathetic approach, the spending of sufficient time to delve into the patient's problems and the constant repetition of the theme of proper living at different visits will repay the effort involved. It is here that the physician can practice the true art of medicine. It is my view that mismanagement arises from the lack of time spent with a patient in going over all aspects of his activities. Since we know of no real way of retarding arteriosclerosis and since we know of no way of predicting when the next coronary attack will come nor whether or not it will be fatal, we should view with grave suspicion any tendencies on our part to impose on him undue prohibitions.

It is the experience of all that undue exertion and undue emotion may precipitate angina and even a myocardial infarct. The particular circumstances that seem to act as trigger mechanisms for angina should be thoroughly explored in each case and ways devised to avoid them.

Many times the trigger mechanism involved in angina is paroxysmal tachycardia, paroxysmal auricular fibrillation or flutter, and, even more commonly, frequent premature systoles. It is for this reason that quinidine has proved so valuable prophylactically. Quinidine is perhaps the best "soothing" agent for ectopic rhythms. It is therefore one of the best drugs available prophylactically in chronic coronary disease complicated by ectopic rhythms. Papaverine works in a similar fashion on ventricular ectopic rhythms; in addition, it is a sedative which is not habit forming and it is a powerful coronary vasodilator. It too, like quinidine, should be employed more often prophylactically than it has been. Xanthines, on the contrary, are used far too often. Of all the xanthines, the only one that appears to work by mouth in my experience, is theocalcin, and this I attribute to the calcium. Xanthines are ordinarily combined with a barbiturate and the barbiturate of the combination is the effective agent. Barbiturates are used alone for sedation and as hypnotics.

Tobacco should be discouraged in coronary disease. It leads to vascular narrowing, presumably including the coronary vessels. Alcohol on the contrary should be encouraged. Port wine is a good hypnotic. A cocktail or two can make many people see life in a more pleasant manner and helps

them to relax. Wines with meals should be encouraged. Alcohol leads to dilatation of blood vessels and presumably this affects the coronary arteries as well. I find that permission by the physician for the patient to indulge in alcohol makes other restraints more tolerable. As to diet the key is moderation. There is no specific food which needs to be avoided. The patient, however, should reduce his weight when he is overweight. When the "coronary" patient has diabetes, the diabetes should be treated moderately. We have found that rigid control of the diabetes actually leads to more frequent anginal attacks and when the control is less rigid the patients do better.

Rest is an important item in management. Some people do well when they are encouraged to take a rest period (or even a nap) during the day. It breaks the tension under which the high powered executive lives. Frequent excursions and holidays are in order. The patient should undertake to keep himself fit by a program of graded exercise. This may include walking, golf and similar activities. These should be indulged in up to the point of tolerance, that is short of the point of fatigue, pain or shortness of breath. Inactivity makes even the healthy person physically unfit. One cannot avoid peaks of exertion or emotional stress in the environment in which most of us live. This is true also of the patient with coronary disease who does not lead an entirely sheltered life, and most of them should not. It, therefore, behooves the patient to put himself in as good a physical condition as possible. When properly carried out, it is amazing how much improvement in physical capacity can be attained. In this program of graded exercise, caution should be used. A sense of competition even with his own par, should be avoided. Any competitive exercise, which tends to make individuals do more than they should, should be avoided. The patient should be encouraged to stop his effort when he feels he has had enough. Incidentally, a game of cards may, by its competitive character, be more harmful than a long walk or fishing!

The nitrites are extremely useful in coronary insufficiency. Nitroglycerine has stood up best of all. Patients soon learn how to help alleviate their anginal attacks with nitroglycerine under the tongue. Nitroglycerine, furthermore, may be employed prophylactically. It may be taken a half hour before an interview or other activity which the patient can not avoid and which he has found is apt to lead to anginal attack.

The handling of congestive heart failure complicating coronary disease is no different from the treatment of congestive failure of any origin and there are no contraindications to the use of digitalis or mercurial diuretics, provided there is an indication for their employment.

Status angiosus may require protracted bed rest. It is amazing how often a period of bed rest at home or in the hospital improves the condition of the patient for a period long after the rest has been completed. When rest is ineffective, alcohol injection of the left (or right) stellate ganglion may lead to remarkable alleviation of status angiosus. It does not remove all the

warning signals of overactivity. The patient should be taught to look for dyspnea, fatigue and other signs indicating that he is doing too much to replace his dependence on pain as a warning. Total thyroidectomy and the Beck operation have not come up to expectations and are rarely if ever justified for angina pectoris.

My dissertation would not be complete without some remarks on the management of recent myocardial infarction. First, I wish to stress that one should sharply distinguish between chronic coronary insufficiency, an anginal attack and an old healed infarct on the one hand, and a recent myocardial infarct on the other. This is true not only clinically but also in interpreting electrocardiograms. Too many men in reading an electrocardiogram showing coronary pattern, jump to the conclusion that this is evidence of a recent infarct and fail to check this deduction by taking seriatim curves, which tend to distinguish the recent myocardial infarct from other forms of coronary disease. The real abuse of bed rest is to put a patient to bed for six or more weeks when the evidence is not clearcut that he has a recent infarct.

Rest is still the best form of therapy for a recent myocardial infarction. The rest should be complete for two or three weeks and may have to be complete for up to six weeks. Even at rest the heart does work. If healing is to be facilitated one should not superimpose an additional load upon the heart which comes from incomplete bed rest. It may be necessary, when orthopnea is troublesome or when the patient is uncomfortable flat on his back, to raise the head of the bed or even to permit the patient to have his rest sitting in an easy chair. Likewise it may be necessary when a patient has difficulty in using a bed pan to permit him to use a commode at the bed side. The aim in treatment is not so much *bed* rest as the approach to complete and comfortable rest. After the period of complete bed rest the length of which is determined by the clinical evolution and the rate of healing revealed in the electrocardiogram, the patient is permitted gradually to sit up, to use a wheel chair and then to get up and about. He then should have a holiday of a month or more before being permitted to resume his normal activities with certain restrictions. The overall time before normal activities on a restricted scale can be resumed is variable, but ordinarily is a matter of three to six months at most.

Recently considerable discussion has arisen in regard to the abuse of rest in recent myocardial infarction because of the hazards of hypostatic pneumonia, bed sores, and venous thrombosis and pulmonary embolism. These are real hazards but not as frequent as some would have us believe. They are most apt to occur in debilitated and in elderly patients. Hypostatic pneumonia can be avoided by shifting the position of the patient from time to time. Voluntary deep breathing periodically also has been suggested as a preventive measure. Thromboembolic phenomena are a much more serious complication. Massage of the legs and their movement by the patient from

time to time may be employed to prevent thrombosis. Recently, anticoagulants in the form of dicumarol have been suggested for this purpose. While the results are not conclusive and a study devoted to the evaluation of dicumarol is now being pursued in a number of institutions under the auspices of the American Heart Association, sufficient evidence has accumulated to suggest that this method of therapy is effective. The number of thromboembolic phenomena and fatalities complicating myocardial infarction are sharply reduced by anticoagulant therapy when carried out under hospital management with a careful assay of prothrombin times during the course of treatment. It appears that there is a real likelihood that this will be a definite advance in the management of recent myocardial infarction. I would be prepared to state at the present time that any patient who shows a thromboembolic episode after a recent myocardial infarction deserves to be placed upon dicumarol therapy. It may turn out that every patient with a recent myocardial infarction should receive this form of therapy prophylactically, during the period of bed rest following infarction. However, the final decision on this latter point will have to await the final report of current studies.

Shock is one of the serious complications of recent myocardial infarction. It should be distinguished from the immediate vascular collapse which often accompanies infarction. Dr. Brams of our hospital, in some as yet unpublished studies, has found that desoxyephedrine, on several occasions, has had a remarkable effect in counteracting the vascular collapse of myocardial infarction. If further experience verifies this finding, it may become a useful addition to our armamentarium. Shock, following recent infarction, and by this I mean the same kind of syndrome which follows trauma and surgery, should be handled like shock of any other origin. Blood transfusions, administered at a rate slow enough to avoid burdening the heart, have been found useful in avoiding the irreversible stage and death. They should not be given when there is evidence of pulmonary edema or when the systemic venous pressure is elevated. When transfusions are given the patient should be carefully observed during administration to avoid evidences of pulmonary or systemic venous engorgement. Collapse and shock are serious complications and are apt to result in death of the patient, when untreated. The use of pressor drugs and of blood transfusions are heroic procedures to avoid these end results, and their employment is therefore a matter of weighing risks.

The appearance of paroxysmal rapid heart action requires treatment. Such rapid heart action is a burden on the already weakened infarcted heart. Paroxysmal auricular fibrillation can be treated with strophanthin intravenously. Paroxysmal auricular tachycardia and paroxysmal auricular flutter can be treated with quinidine. Frequent ventricular premature systoles occurring during the course of infarction require the employment of

quinidine, or of papaverine, or of both. Paroxysmal ventricular tachycardia requires heroic therapy, either oral quinidine or papaverine intravenously.

It is well recognized that morphine is an extremely useful drug in recent myocardial infarction. Occasionally demerol may be used in its place. Some people advocate the use of atropine, and this drug may be useful in preventing reflexogenic ectopic rhythms. I still believe that, even in the absence of ectopic rhythms, papaverine is a useful drug in recent myocardial infarction provided it is used in high enough doses. However, it must be pointed out that it appears to be ineffective in some cases and in others it leads to unpleasant side actions.

The question of oxygen therapy is constantly raised. It is indicated whenever pulmonary edema or pulmonary congestion is present. I am not so sure that it should be used in every case of recent myocardial infarction. Of course, it can do no harm except for the fact that to many patients it carries the implication that they are moribund. Some patients develop a sense of claustrophobia when they are placed in an oxygen tent. I believe that the nasal catheter is too irritating to be employed ordinarily; it often leads to irritation or inflammation of the pharynx which causes hacking and coughing, both undesirable efforts. Of all methods of administering oxygen probably the best is the use of a mask such as was employed in the Air Forces in high altitude flying.

When diabetes complicates a recent myocardial infarction the proper use of insulin and sugar will avoid ketosis. The treatment, however, must not be aimed at making the patient sugar free. A little sugar spilled in the urine is not dangerous.

Congestive heart failure often complicates recent myocardial infarction and it should be handled exactly like congestive failure of any other cause. In fact, the use of mercurial diuretics and of digitalis should be vigorously pursued. Digitalis is not contraindicated in recent myocardial infarction. It does not lead to coronary constriction except in toxic doses, and it does not lead to rupture of the heart. Digitalis should be given to relieve the congestion and should be stopped or reduced when this effect is obtained or when toxic symptoms appear.

In this survey I have tried to cover only a few of the main points in recent concepts of coronary disease and its management. Obviously I have dealt with many a controversial aspect and have presented a number of matters which are still being investigated. I have not hesitated to express my own views, realizing full well that in many places I am not in accord with current beliefs and fads. I have done so because these are my convictions, based on a survey of the literature and personal experience in the laboratory and as an observer and experimenter at the bedside. In closing, I would like to emphasize once again that, great as has been our advances in this important affliction of man, there is still need for much further

exploration. If the next decade will be as fruitful as the last, we can surely say that our concepts in management of coronary disease will advance tremendously. The ultimate solution, however, which should resolve this problem is one of basic research seeking to answer the query—what is the cause of atherosclerosis? Furthermore, we need some knowledge regarding the manner in which atherosclerosis can be retarded, and it is not too much to believe that ultimately, perhaps in our lifetime, we will know how to prevent atherosclerosis and thus finally to allow people to die merely of real old age.

ALLERGY: TRENDS AND THEIR IMPLICATIONS *

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The procedures in the present day management of some of the allergic manifestations are chiefly the result of concepts and experimental findings established many years earlier. The chief events responsible for the development of the practice of allergy have been: the demonstration of anaphylactic phenomena at the turn of this century by Hericourt and Richet,[1] Arthus [2] and others; the concept of bacterial allergy advanced by Von Pirquet [3]; the production of the refractory state, or desensitization, in sensitized animals; the attention called by such men as Wolff-Eisner [4] and Meltzer [5] to the resemblance of hay fever and asthma to the anaphylactic symptoms in the guinea pig; and the demonstration of diagnostic possibilities of the whealing skin reaction by Blackley,[6] Schloss,[7] and others. Later, the demonstration of the specific antibody in allergy, the atopic reagin,[8] gave us the explanation of a part of the mechanism of the allergic reaction. Still later, the finding of another antibody, the blocking antibody,[9] which prevented the union of antigen and reagin, gave us the first immunological evidence in support of the mechanism of desensitization in man. These facts, applied first to the etiology, diagnosis and specific treatment of asthma and hay fever, were extended to other conditions such as eczema, contact dermatitis, migraine, urticaria, gastrointestinal manifestations, ophthalmologic diseases and other conditions.

In more recent years certain trends have been emerging in the field of allergy with respect to its practice, its attitudes, its thinking and its concepts. These trends will undoubtedly play a prominent part in the molding of the science and the practice of allergy of the future. It is with that thought in mind that I wish to consider with you some of these trends.

Trend of Increasing Practical Interest in Allergy

In recent years there has been a substantial increase in interest in allergy on the part of the medical profession and the public. Many practitioners who knew nothing and cared less about allergy five or 10 years ago are now attempting to apply allergic management to some of their patients. More and more physicians are groping for some basic and practical knowledge which they can apply to the care of at least some of the simpler allergic problems. The popularity of the short intensive courses in allergy given in the last two or three years under the auspices of the national specialty so-

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cieties, the American College of Physicians, and other groups, is one of the bits of evidence of that trend. In undergraduate teaching in many of the medical schools more attention is being given to the subject of allergy.[10] The rapid increase in the number of local and regional societies and the growth of the national societies are indications of professional interest. The number of qualified specialists in allergy is on the increase, but the requests for the proper training enabling the candidate to fulfill the specifications of the Boards of Internal Medicine, Pediatrics and Allergy, exceed the available facilities.

The public, too, has become familiar with the word "allergy" and its application. The radio, the newspaper and other forms of communication now speak freely of allergy, without even bothering to define it. Indeed, newspaper and radio reports are so intent on reporting new medical developments that often the doctor is in the embarrassing situation of having his patient bring a so-called discovery to him. Adding further to the interest in allergy among many individuals are the growing problems of occupational allergic disease and the allergic manifestations resulting from an ever increasing array of therapeutic agents.

Trend Toward Misdirection of Principles of Allergy

One could write a volume on an elaboration of the misconceptions and misapplications in the field of allergy. I shall call attention briefly to but a few of the misunderstandings resulting in misdirection. Drugs and symptomatic remedies are often used as if they were cures instead of simple palliative measures. Nose drops do not remove the underlying nasal allergy: as a matter of fact, the more potent nasal vasoconstrictors may increase the congestion.[11] The new antihistaminic drugs on the market in the last year or two, and other similar drugs now in the experimental phase, are at best only palliative remedies.[12] In the meanwhile they are prescribed in conditions in which other drugs are more helpful and in conditions which have nothing to do with allergy.

Those who do not wish to deal with the detailed and sometimes tedious procedures and problems of the allergic patient often solve the difficulty, for themselves if not for the patient, by recommending a change of climate. Such changes of climate may be indicated for patients in whom, after proper and adequate allergic and other studies, there is reasonable expectation of benefit from such a change. But, promiscuous advice for asthmatic people to "go west" is unscientific and unjust. Misdirection in surgery of the nose and throat for the treatment of allergy is fortunately not as common now as it was a number of years ago.

In the matter of specific allergic management there are still many misunderstandings and misdirections. The common fault of considering every positive skin test as indicative of a clinical allergy to that substance results in unnecessary procedures, deprivations and detraction of emphasis from

more useful steps. The common misconception that negative skin tests rule out an allergic etiology constitutes another large source of error in diagnosis. Many clinicians fail to understand that, unlike in anaphylaxis, desensitization in human allergy is only partial, slow in achievement and not permanent. Unless the patient is made aware of this situation in the beginning of his management, disappointment and discouragement are likely to result. There is still a tendency to give injections of antigens based solely on the skin reaction and a further tendency to neglect the important principle of individualization of dosage schedules.[13, 14] In the attempt to broaden the scope of allergy there results at times the misdirection of applying practical allergic procedures to conditions for which there is only a theoretical allergic concept.

Medicine as a whole is now in a psychosomatic era and allergy is sharing this reflected influence. It is interesting to note that many years ago, before the advent of the bacteriologic era, the psychogenic or nervous theories of disease were in vogue. The present tendency is more or less a revival. Chronically allergic persons do become nervous and develop psychic complexes, and it is true that intensive nervous or psychoneurotic states may aggravate an allergic manifestation. But we have a strong conviction that consigning the etiology of many of the common allergic conditions to a "psychosomatic" explanation constitutes merely an avoidance of the challenge which the solution of the problem entails.

One of the most outstanding characteristics of the present day practice of allergy is the skepticism with which it is regarded by many lay people and physicians. This trend is due in large part to the numerous misconceptions about allergy, some of which I have mentioned in the foregoing discussion. But perhaps the most important cause for this attitude is the fact that these particular people have been led to expect from allergic procedures 100 per cent results in diagnosis and therapy. Now, no one expects such perfection in the management of chronic diseases such as diabetes, hypertension, arthritis and heart disease. But the very dramatic and complete eradication of allergic manifestations which is possible in some instances has led to the hope that this would be attainable in all. The science of allergy is far from this goal, and it is important that physicians as well as lay people should be aware of this so that the field will not be discredited.

Trend Toward Extension of Scope of Allergy

Interest in allergic phenomena of bacterial infection is beginning to attract more serious attention from capable investigators. The early demonstration of the phenomena of bacterial hypersensitiveness in tuberculosis had led to the extension of this principle to a study of other infectious diseases, but it is remarkable how this phase of research lagged until comparatively recently. Rheumatic fever is one of the examples in which interest in the allergic concept has been prominent. As far back as 1902 Meltzer advanced

the theory that acute articular rheumatism was an allergic manifestation. Weintraub then claimed that rheumatic fever constituted an anaphylactic phenomenon resulting from a reaction to bacterial proteins. Swift and his associates [15] have done extensive experiments which indicate that some of the manifestations of rheumatic fever are due to an allergy to the nonhemolytic streptococcus. The tissue alterations in hypersensitive rabbits and the pathological changes in rheumatic fever are now regarded by many pathologists as strikingly similar. Recently, Rich and Gregory [16] showed that the cardiac lesions produced in rabbits as a result of serum sickness resembled the typical Aschoff bodies of rheumatic fever. Space does not permit the discussion of a number of other infectious diseases in which the allergic concept is receiving attention.

In recent years a number of other pathologic states have been seriously discussed as allergic phenomena. We shall mention only one or two of these. In 1925 Gruber [17] suggested that periarteritis nodosa might be an allergic disease. His claim was based in large part on the presence of eosinophilic infiltrations. Later the allergic concept was strengthened by the reports of the association of asthma with periarteritis nodosa and the finding of high percentages of blood eosinophilia in these patients. Rich and Gregory [18] reported lesions of periarteritis nodosa in patients who died after having had serum sickness or allergic reactions to sulfonamides. When these investigators succeeded in producing similar lesions in rabbits after serum sickness [19] the evidence for the allergic nature of periarteritis nodosa seemed to be fairly complete.

Acute disseminated lupus erythematosus, long regarded as a disease of unknown etiology, is now linked with the concept of allergy by a number of pathologists and other investigators. Fibrinoid degeneration of connective tissue is found by Klemperer and his associates [20] and others to be the outstanding pathologic change in this disease. This degeneration of the collagen is considered by some as a common factor linking this disease with scleroderma and dermatomyositis. Fox [21] reported a case of lupus erythematosus in a girl after serum administration. Teilum [22] presents evidence from the University Institute of Pathological Anatomy at Copenhagen that lupus erythematosus disseminatus is an allergic state, probably due to hypersensitiveness to various bacteria and their allergenic substances. He describes the miliary epithelioid cell granuloma in the serosa as the typical lesion and the primary fibrinoid degeneration of the collagen as the factor common to this disease and rheumatic fever. In dermatomyositis the itching and edema can be presumably explained on the basis of histamine release, although there has been no proof of that. It was interesting to note, however, that we obtained decided relief of the itching in a case of dermatomyositis with the use of one of the antihistaminic agents, pyribenzamine.

Trend Toward Changing Immunologic Concepts

The early concept confining the antigen to proteins, especially of large molecular size, is undergoing considerable evolution which is bound to have theoretical as well as practical implications in allergy. Many years ago Landsteiner [23] and his followers demonstrated that a nonprotein substance of small molecular weight could be endowed with specific antigenic properties if it were attached to a larger molecule, usually a protein. This was the hapten concept which gave rise to the current explanations offered for many of the types of drug allergy. In passing, it must be emphasized that as yet there is no conclusive proof that this hapten conjugation in vivo is the modus operandi in drug allergy. The researches of Heidelberger, and Avery and others then demonstrated without a doubt that complex carbohydrates could also constitute antigens, having many of the properties of protein antigens. Some evidence has also been advanced which indicates that even lipoids can be antigenic.

Then there began to emerge reports here and there indicating that chemical substances of low molecular weight can have antigenic properties. In some instances animals were sensitized with such substances, while in others the manifestations of hypersensitivity were produced by the reapplication of such a chemical. In a series of patients having occupational exposure to a chemical substance of low molecular weight (chloramine) we were able to show not only that it was capable of producing asthmatic symptoms but also that it was able to give specific whealing skin reactions and displayed circulating antibodies.[24] Unless it can be shown that there is a conjugation of this substance in the body, the implication is evident that small molecules can constitute complete antigens and can produce allergy.

And if this latter possibility is correct we shall have to modify our entire attitude toward the search for causes of allergic manifestations. Our current procedures are definitely those aimed at disclosing protein allergy and skin reacting antigens practically exclusively. It is not beyond the stretch of the imagination that we might have to reroute our efforts and technics to include investigations seeking to suspect as allergens the various and relatively simple chemical substances, which may or may not be skin reacting, in foods, coal smoke and other contaminants released in the atmosphere, particularly from industrial plants. As a matter of fact, many clinical observations in allergic patients, such as the bronchospastic effects of coal smoke, some of the benefits of climatic change, and the presence of many cases of allergy with unidentified causes, strengthen the suspicion that atmospheric contaminants may be an important class of allergens.

There are other immunologic studies in progress that may ultimately have a profound influence on the practice and success of allergy. Among these may be mentioned advancement in our knowledge of the nature of antibodies and antigens, and attempts aiming at the improvement and perfection of methods of immunization.

Trend Toward Increasing Man-Made Allergy

Beginning primarily with the use of animal serums in medicine, the problem of allergy to therapeutic substances has been rapidly increasing. The countless allergic reactions from the arsphenamines, the allergic reactions from insulin and liver extracts, injectable hormones and vitamins, and the numerous allergic manifestations from the sulfonamides, barbiturates and antibiotics, constitute an incomplete list of our multiplying allergic hazards with each new therapeutic advance.

The range of therapeutic substances is so broad that no practitioner of medicine, whatever his specialty, is now immune from contact with allergic experience. It is in large part these man-made allergic problems which have forced all medical men to the necessity of becoming conversant with some of the phenomena of allergy. We are presented with a problem which is going to increase in importance with the further rapid development of new therapeutic products. It is difficult to say what the final outcome of this situation will be and how we shall learn to combat it. In the meanwhile, a practical and sane attitude should be to discourage the use of sulfonamides, penicillin and other sensitizing agents in trivial ailments, so that the patient will less likely be allergic to that drug when he is in desperate need of it.

Scientific and practical progress in the field of drug allergy might be made more readily because it lends itself to close study, since we are dealing with a group of allergic manifestations in which the etiologic agent is identified and its chemistry known. The phenomena of drug allergy open greater opportunities for observations on the immunologic mechanisms and processes of allergy in general.

Trend Toward a Single Therapy for All Allergy

The concept of a nonspecific method for the production of specific immunologic response is not new. Hundreds of forms of nonspecific therapy have been advocated from time to time, and some are still in use. For the most part they have been complete failures or impractical of application. In the last decade or so various efforts have been directed at combating the histamine effects of the allergic reaction. The hope that histaminase could be an effective agent has now been dimmed.[25] Although in proper proportions in vitro when in contact for a number of hours histaminase will destroy histamine, the conditions in the living animal are entirely different and such therapy has been judged as useless. Histamine itself does not produce a tolerance to histamine,[26] and critical observers [27] now agree that histamine-azo-protein, meant to increase the tolerance to histamine, also fails in its objective.

At present we are in an era of active interest in anti-histaminic agents. For a number of years investigative work has been going on with the idea of synthesizing compounds which would have competitive action with his-

tamine for cell receptors. As a result of these researches some drugs have been found sufficiently useful to be made available to the general medical profession. Such drugs used clinically in this country are benadryl and pyribenzamine,[12] while in Europe neoantergan [28] and antistine [29] are the representatives in this field.

These drugs are similar in their action, although there are some differences in their quantitative effect and in the intensity of their toxic symptoms. In general, they are effective in the symptomatic relief of a large percentage of patients with urticaria, angioneurotic edema and seasonal hay fever, and are helpful in a lesser percentage of cases of chronic vasomotor rhinitis. They are also useful in eczema and in other forms of itching, such as pruritus ani or vulvae. Their effectiveness in asthma is very slight and rarely reaches the degree of action obtained from epinephrine, ephedrine or aminophyllin.

The fanfare and publicity which accompany the launching of new drugs in our modern times are almost certain to result in the misuse of such drugs. It takes a long while before all medical men and the public learn from experience that initial enthusiasm must be deflated and the limitations of the drug defined. The antihistaminic drugs are still in the phase of enthusiasm. Many allergic conditions for which they are put to use are known to respond very little, if at all to them. Many other conditions for which there is no allergic concept are also being subjected to these drugs, for no other reason than that a new therapeutic agent is available.

All of these histamine antagonists, and other new ones with which we have been experimenting, produce undesirable side reactions, in greater or lesser degree. The most common side reaction is sedation or sleepiness. This is most marked in the case of benadryl and varies with the other drugs. Other side reactions have been dizziness, palpitation, nausea, nervousness, lassitude and insomnia. In many instances these side actions are of sufficient order to make it inadvisable for the patient to continue the use of the drug. More severe toxic effects, such as convulsions, have been also noted. The possibility of remote toxic effects from these drugs is still not a settled question, although there appears to be no decided tendency to it.

These drugs are of some aid in the treatment of allergic manifestations, but it should be noted that they possess objectionable features also. Attempts are being made to produce still newer drugs which will be less toxic, and we are now experimenting with some of these. It must be emphasized, however, that the most perfect of such drugs would only be palliative and should not be confused with the more lasting relief possible by specific desensitization.

The search for an ideal antihistaminic substance has constituted the most decided trend in recent years in the investigation of antiallergic therapy. However, some of our experimental findings in the investigation of antihistaminic agents indicate that there is no direct quantitative relationship

between antihistaminic, antianaphylactic and antiallergic potency. These and other considerations furnish the basis for the belief that other mechanisms in addition to histamine release may be important components of the anaphylactic and allergic reaction. It is necessary, therefore, in the future in the search for antiallergic drugs to use other screening methods in addition to antihistamine activity.

Other Trends in Scientific Progress in Allergy

There has always been the necessity and now there is a growing inclination for the allergist to observe and examine the developments in other fields of science so that he may apply them to his own investigations. One of the most fertile fields, of course, is immunology. We have already discussed a few of the immunological phases of interest to allergy. At this point mention should be made of another general trend in allergy and immunology. This may be called the trend for unification. Facts are emerging which tend to decrease the breach between allergic manifestations which had been regarded in the past as totally unrelated. For example, one of the prime differences between atopic allergy, such as in asthma, and bacterial allergy, such as in tuberculosis, had been the failure to find transferable antibodies in the latter. And now with the demonstration that the leukocytes can transfer bacterial allergy the two types of allergic manifestations are brought closer.

In the past the anaphylactic antibody had been sharply delineated from the human allergic antibody. New experimental facts are approximating these antibodies. There is an increasing trend to regard different types of antigens producing different allergic manifestations as behaving in a similar manner. It has also been shown that a number of specific antibodies can be present in the same protein molecule.

Many of the achievements in other scientific fields may contain the clue to the solution of some of our allergic problems. From the facts of physics we are learning how to modify antigens for slower absorption. The development of our knowledge of isotopes should enable us to learn about the fate of antigens and antibodies, the behavior of histamine and many other facts of importance in allergy. The new work of Tiselius on the separation and identification of proteins, peptides, amino acids and other substances by physical adsorption should open the way for many investigations dealing with immunology and allergy.

Summary

Allergy is attracting increasing interest from the public and medical profession. Because of that we must give greater attention to a consideration of the elementary facts concerning it so that the tendency to misdirection will be minimized. The growing problem of allergy to drugs and injectable substances is forcing almost every practitioner to become conversant with the

field. There is a decided trend to the realization that the concept of allergy is important in the interpretation of the phenomena of many of the infectious diseases. Progress in the synthesis of antihistaminic drugs probably represents only one phase of the trend to attack basic problems in allergy.

There is a growing tendency for those interested in allergy to apply immunologic, pathologic, physiologic, physical and chemical discoveries and methods to advance this science. The field of allergy needs, and holds great promise for, competent clinicians and particularly those who have an imaginative and pioneering spirit. For such men and women many of us will make great effort to provide the requisite stimulation, training and experience.

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SPLENOMEGALY IN CONGESTIVE HEART FAILURE *

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During the past few years, we have noted several instances of palpable spleen in patients with chronic cardiac decompensation; no other reason for splenic enlargement was found in these cases.

It has long been a general impression that the spleen does not become palpably enlarged as a result of congestive heart failure alone. As a corollary of this, it has been felt further that if the spleen is palpable in a case of heart failure, some complication should be suspected. This statement was made by Held [1] in his discussion on splenomegaly, and the same opinion was voiced by Rolleston.[2] Talley and Lindsey [3] studied 198 adults with congestive heart failure, and found palpable spleens in only three. Comroe [4] did not list congestive failure as a cause of splenomegaly in adults. Fishberg [5] stated that it is doubtful that the spleen ever becomes palpable in congestive failure alone, but admitted that changes in the liver secondary to cardiac decompensation may produce a spleen that is sufficiently enlarged to be felt. He also said that the spleen is often small and atrophic in long-standing congestive failure. Similar statements were made by Boyd [6] and MacCallum.[7] Klemperer [8] indicated that the spleen is occasionally enlarged in congestive failure of great duration, but that it is often smaller than normal. Ravenna [9] made a similar comment.

However, not all writers have agreed with these views. Barker [10] has reported a case of rheumatic heart disease in chronic decompensation with a palpable spleen. There were no apparent complications in his case. Barron and Litman [11] found spleens weighing over 300 grams in 10.4 per cent of 1505 autopsied cases of chronic cardiac disease. Arnett [12] found the spleen enlarged in 23 per cent of cases of chronic non-infectious heart disease.

With the above points in mind, a review was made of the records of the Department of Pathology at the Peter Bent Brigham Hospital. All cases were selected from admissions to the medical and surgical wards of the Peter Bent Brigham Hospital who subsequently came to autopsy. The cases selected were divided into four groups. The first group is composed of 50 patients from the surgical service. These were used to determine the normal average weight of the spleen. Cases of congestive heart failure, myocardial infarction, or in whom congestion of the viscera was diagnosed pathologically are excluded from this group. The second group comprises 50 cases of valvular rheumatic heart disease; only cases with both clinical and pathological evidence of congestive heart failure were included in this group. The

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third group is composed of 50 cases of hypertensive or arteriosclerotic heart disease diagnosed pathologically or clinically and confirmed at necropsy. The fourth group comprises 46 cases of subacute bacterial endocarditis. These were included in order to determine the relative size of the spleen in this disease, in which the frequent occurrence of a palpable spleen is widely recognized. Patients under 16 years of age were not included. Cases in which there was found either clinical or pathological evidence of diseases often associated with splenomegaly were excluded. Subacute bacterial endocarditis was excluded from the first three groups. Also excluded were cases not admitted to the wards, cases in which the spleen was not weighed, and five cases in which the necessary pathological data were not available. Patients with congestive failure of less than one month's duration, and those having a recent myocardial infarction as the only cause of decompensation were omitted.

TABLE I

	Group 1. 50 Surg. Cases Normal?	Group 2. 50 Rheum. Heart Disease	47 Rheum. Heart Disease	Group 3. 50 Non-Valvular Heart Disease	Group 4. 46 Sub. Bact. Endocarditis
Average weight of spleen in grams	135	220	210	198	371
Number spleens over 200 grams	9	23	20	19	39
Number of spleens over 300 grams	None	9	7	6	30
Number spleens infarcted	—	8	8	6	22
Average weight infarcted spleens in grams	—	239	239	197	—
Average weight of spleen in cases with failure 3 years or over	—	—	228 (31 cases)	190 (14 cases)	—
Average weight pt. in kg.	68 (36 cases)	—	67 (34 cases)	71 (32 cases)	68 (40 cases)
Average age pt. in years	56	47	—	56	—
Number livers over 1600 grams	—	19	16	20	—
Number livers over 1900 grams	—	9	7	11	—
Average weight liver in grams	—	1487	1460	1608 (49 cases)	—

In all cases of congestive failure, the weight and histology of both spleen and liver were noted. When available, the ages and weights of patients in all groups were recorded, since both these factors influence spleen size.[13] Weights were taken from a period of relative good health. The duration of the symptoms of congestive failure was also recorded, in order to determine whether this is a factor influencing the size of the spleen.

Findings. Results are summarized in table 1. The average spleen size in the surgical control group was found to be 135 grams. In the 50 cases of rheumatic valvular heart disease, the average spleen weight was 220

grams. Excluding the three cases of microscopic biliary cirrhosis found in this group, the average spleen weight fell to 210 grams. In the hypertensive and arteriosclerotic heart disease group, the average weight was 198 grams. In subacute bacterial endocarditis, the average was 371 grams.

Barron and Litman,[11] in their study on hepatomegaly and splenomegaly, considered any spleen over 200 grams to be enlarged, and any of 300 grams weight or more, to be in the range of clinical palpability. Fifteen per cent of the spleens in the entire congestive failure group were in the range of theoretical palpability; upon exclusion of the three cases of biliary cirrhosis, this figure falls to 13.4 per cent. It is of interest to note that only one of these 15 spleens was actually felt on the ward, although one weighed 700 grams, another 625 grams, and another 500. This is probably explicable on the basis that these patients were examined within a few days or weeks of death and were unable to coöperate; in addition to this, most were orthopneic, and many had ascites and edema of the abdominal wall. Still another factor hindering the palpation of the spleen in a patient with cardiac decompensation is his impaired vital capacity and inability to move his diaphragm fully. The ages and weights of the patients in the first three groups were felt to be sufficiently similar to permit of their elimination as a factor in determining the size of the spleen. Duration and type (i.e. valvular or non-valvular heart disease) seemed to play no great part in determining the weight of the spleen at autopsy. Among the cases of rheumatic heart disease, there were eight showing splenic infarctions; in these the average spleen weight was 239 grams. Splenic infarctions were found in six of the non-valvular heart disease group; here, the average spleen weight was 197 grams. In neither instance did the presence of infarctions seem to play a great part in influencing the weight of the spleen.

In the rheumatic valvular group, cardiac cirrhosis was found in 11 instances; in these, the average spleen weight was 300 grams, considerably above the group average. All these patients had histories of congestive failure for at least six months prior to death, and the average duration of their failure was 4.6 years. If the cases of biliary cirrhosis, two of whom also had cardiac cirrhosis, are removed from this group, then the average weight of the spleen falls to 274 grams. Only one case of cardiac cirrhosis was found in the non-valvular heart disease group; here the spleen weighed 420 grams.

Barron and Litman [11] found spleens weighing over 300 grams in 85 per cent of 87 cases of subacute bacterial endocarditis. Blumer [14] determined that 74 per cent of 220 cases of subacute bacterial endocarditis showed splenic enlargement by either palpation or percussion. Arnett [12] found at autopsy that 51 per cent of the spleens in his series were enlarged in this disease. He used as his criterion of splenic enlargement an increase of 50 per cent above the average size. In this group of 46 cases of subacute bacterial endocarditis, spleens weighing over 300 grams were found in 65.2 per cent of the cases.

Gray [15] considers 1600 grams to be the upper limit of weight for the normal liver; Barron and Litman [11] give 1900 grams as their upper normal for this organ. By their standards, Barron and Litman [11] found hepatic enlargement in only 8.5 per cent of their 1505 cases of heart disease, but found splenic enlargement in 10.4 per cent of these cases. Arnett [12] found 23 per cent of the spleens enlarged in chronic cardiac disease, but livers enlarged in only 17 per cent, using an increase of 30 per cent above the average as his criterion of hepatic enlargement. Smith and Levine [16] found the average weight of the liver in 32 cases of tricuspid stenosis to be only 1535 grams. The number of livers exceeding 1600 grams and exceeding 1900 grams in the cases of congestive failure in this series is given in table 1. It is of interest to note that the weight of the average liver in the hundred cases of congestive failure is not above normal. The fact that the liver is frequently felt clinically in congestive heart failure, and yet is not on the average enlarged by weight at necropsy is difficult to explain. Ptosis of the liver may be one factor involved in this apparent paradox. Probably a more important factor is the loss of blood from the liver before it is weighed in the course of a postmortem examination.

Summary and Conclusions

1. The spleen, on the average, is increased above the normal size in uncomplicated heart failure.

2. The splenomegaly of cardiac decompensation is apparently not greatly influenced by either the duration of the congestive failure nor by the presence of infarctions in the spleen.

3. In 13.4 per cent of 97 cases of uncomplicated congestive failure, the spleen was found to be large enough to be theoretically palpable, i.e., over 300 grams.

4. The spleen, on the average, shows greater enlargement than does the average liver in cardiac decompensation.

5. Other than actual congestion of the spleen and the presence of cardiac cirrhosis in the liver, no satisfactory explanation for the occurrence of splenomegaly in congestive heart failure is found.

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PROBABLE GENETIC PREDISPOSITION TO VIRAL PNEUMONIA *

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Observations from time to time suggest unusual susceptibility among members of families to certain infectious diseases. Although it is often difficult to separate hereditary influences from environmental ones, the high incidence of tuberculosis, leprosy, colds,[1] pneumonia,[2] poliomyelitis and especially of rheumatic fever among persons of certain genetic groups seems to depend upon a combination of inherited susceptibility, environment and exposure to common sources or to each other. The following observation of a close succession of attacks of viral pneumonia among females in direct line of descendence seems to portray such an occurrence.

The family group consisted of the grandparents, three daughters and their husbands, and four grandchildren as illustrated in the figure. The grandmother became sick in Florida about January 1, 1946, with chills, fever, headache, sore throat, blocked nose and persistent cough. She returned to her home in Philadelphia January 5, 1946, and was admitted to the hospital January 11, 1946. Between January 5 and 11 her daughters and their husbands were exposed to infection during repeated visits at her bedside, and could obviously have served as indirect carriers of infection to the children in their own homes. The first of the apparent indirect contact infections occurred in granddaughter, S. F., on February 1, between two and three weeks later, which is the supposed incubation period of certain forms of viral pneumonia.[1] In the subsequent 10 days, four other apparent direct or indirect contact infections began. The dates of onset of disease in the six patients and the probable nature of contact were as follows:

Grandmother, M. B., Aged 52, January 1
Granddaughter, S. F., Aged 9, February 1 ..... Indirect Contact
Daughter, B. F., Aged 34, February 2 ..... Direct Contact
Daughter, M. R., Aged 29, February 3 ..... Direct Contact
Daughter, R. S., Aged 31, February 5 ..... Direct Contact
Granddaughter, E. R., Aged 9 mo., February 10 ..... Indirect Contact

The disease was of the severe form in each of the six female patients and no evidence of infection either mild or severe occurred in the six corresponding male members of the exposed family group as shown in the figure, nor did it occur in the immediate community before, during or after the episode. The attacks in all six patients were characterized by the usual features of viral pneumonia with rather sudden onset; dry, persistent, or paroxysmal

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nonproductive cough; dyspnea, cyanosis, high fever, photophobia, sweating, normal number of leukocytes, and roentgen evidence of bilateral pneumonia.[1] One patient, B. F., was alarmingly sick with fever of 40° C. (104° F.) and periods of peripheral vasomotor collapse. The disease lasted from 15 days in E. R., to 39 days in M. B. All recovered uneventfully.

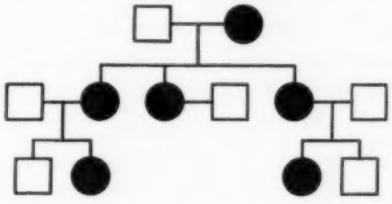

FIG. 1. Members of three generations of a family group. The black discs represent sick females; the squares, the unaffected males.

COMMENT

Although it is impossible to prove the existence of specific genetic susceptibility to viral pneumonia in the patients mentioned, the sequence of attacks in each of the female members in direct line of descendence and the escape of the equally exposed male members whether genetically related or not, strongly suggests its operation. The occurrence represents a localized outbreak of a form of viral pneumonia contracted at a distant place and carried by a patient into a family group. The individual attacks were all severe and no instances of mild, non-pneumonic forms were detected, nor did the disease spread outside the family group. The circumstances further illustrate the contagiousness of the severe sporadic form of viral pneumonia for susceptible persons of various ages and its relatively long incubation period, assuming that M. B. was the direct source of infection for the daughters and the indirect source for the granddaughters.

SUMMARY

Attacks of severe viral pneumonia occurred in close succession in six genetically related female members of a family. Corresponding male members escaped infection. The occurrence suggests that a genetic predisposition to the disease existed in these patients.

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THE MANAGEMENT OF HYPERTENSION *

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In 1892, fifty-five years ago, William Osler,[1] in the first edition of his noted textbook on The Principles and Practice of Medicine, had the following advice to give concerning Bright's disease, with particular reference to cases with "persistent high tension."

"*Treatment.* Patients without local indications or in whom the condition has been accidentally discovered should so regulate their lives as to throw the least possible strain upon heart, arteries, and kidneys. A quiet life without mental worry, with gentle but not excessive exercise, and residence in an equable climate, should be recommended. In addition they should be told to keep the bowels regular, the skin active by a daily tepid bath with friction, and the urinary secretion free by drinking daily a definite amount of either distilled water or some pleasant mineral water. Alcohol should be strictly prohibited. Tea and coffee are allowable.

"The diet should be light and nourishing, and the patient should be warned not to eat excessively, and not to take meat more than once a day. Care in food and drink is probably the most important element in the treatment of these early cases.

"A patient in good circumstances may be urged to go away during the winter months, or, if necessary, to move altogether to a warm equable climate, like that of southern California. There is no doubt of the value in these cases of removal from the changeable, irregular weather which prevails in the temperate regions from November until April.

"At this period medicines are not required unless for certain special symptoms. Patients derive much benefit from an annual visit to certain mineral springs, such as Poland, Bedford, Saratoga, in this country, and Vichy and others in Europe. Mineral waters have no curative influence upon chronic Bright's disease; they simply help the interstitial circulation and keep the drains flushed. In this early stage, when the patient's condition is good, the tension not high, and the quantity of albumen small, medicines are not indicated, since no remedies are known to have the slightest influence upon the progress of the disease. Sooner or later symptoms arise which demand treatment. Of these the following are the most important:—.....

.....

In cases with persistent high tension the diet should be light, an occasional saline purge should be given, and sweating promoted by means of hot air or the hot bath. If these measures do not suffice, nitroglycerin may be tried, beginning with one minim of the one per cent solution three times a day, and gradually increasing the dose if necessary. Patients vary so much in susceptibility to this drug that in each case it must be tested, the limit of dosage being that at which the patient experiences the physiological effect. As much as ten minims of the one per cent solution may be given three times a day. In many cases I have given it in much larger doses for weeks at a time. I have never seen any ill effects from it. If the dose is excessive the patients complain at once of flushing or headache. Its use may be kept up for six or seven weeks, then stopped for a week and resumed. Its value is seen not only in the reduction of the tension, but also in the striking manner in which it relieves the headache, dizziness, and dyspnoea."

* Read at the Annual Meeting of the American College of Physicians, Chicago, April 30, 1947.

Now, in 1947, we are still a long way from what will be the final advice for the treatment or, better still, for the prevention of high blood pressure. And yet, despite our ignorance and our uncertainties during the evolution of our knowledge of this condition and its treatment, it is well now and then to pause a moment and to survey the current attempts to manage hypertension. Hence with no air of finality but with an effort at unprejudiced presentation I shall make some remarks about the treatment of the kind of hypertension that we call essential, the fundamental cause or causes of which are still obscure. I shall not deal with the known causes of high blood pressure or with its common and serious complications, namely hypertensive heart disease and failure, apoplexy, and renal insufficiency. I shall, however, refer to the degree of severity of the hypertension from the transient benign to the sustained malignant and to the relationship to age and arteriosclerosis.

The most important consideration at the start concerns the education of the patient. There are those who believe that it is wisest to conceal from the patient the fact that there is hypertension or at least to hide its severity and never to tell what the actual pressure readings are, except to relatives, especially since so many of these patients are very nervous to start with. I have tried different methods of procedure and have found it more satisfactory in the long run to keep my patients, who are an intelligent lot of people, informed in most instances about the general status of their pressure but with detailed discussion as to its variability and the relative unimportance of the actual figures on any one occasion. To leave the pressure a mystery is usually more worrisome to people than to take them into our confidence, whereby we can also more readily elicit their coöperation in the treatment, especially now-a-days when we can really do something quite effective on occasion. In days gone by when we could do little but palliate, there was some point in discouraging patients from having their blood pressures measured more than once in a dog's age after the initial high reading. Recently in a rereëxamination of cardiovascular rejectees (for the army) originally turned down for military service early in World War II because of hypertension or other cause we found a number of cases with slight hypertension and advised, besides reduction of obesity, an annual or even semi-annual check-up of the blood pressure in the future to catch a more serious rise and then to institute more specific treatment.

The next consideration is that of the way of life and the regimen to be advised. This will, of course, vary greatly from slight restrictions only, if the pressure is borderline or but little increased, to complete rest for extreme hypertension with threatened failure of heart, brain, or kidneys. In general, it is still found helpful to establish a program of leisure, if such is possible, for routine daily living or at any rate to insist on frequent rests or vacations which may come at weekends, long or short, monthly, or for a week or two at a time every three months. The hours of work and the intensity of work should both be reduced; it may be necessary, for example, to advise

doing two or three hours of work daily in four or six hours, or four hours in eight, instead of what is so common to these individuals, namely crowding 24 hours into 12 or 16 every day.

A pleasant prescription of ancient vintage is to order a three or four weeks' stay at the baths somewhere twice a year. Thus at some delightful spot in the country with well regulated diet, rest, exercise, and baths many thousands of patients with hypertension have, doubtless for centuries, kept their pressure under fair control and may very well have avoided the need of more radical measures now in vogue. Last summer in Czechoslovakia I visited many famous spas, some with special reputation for helping hypertensive patients. Mackenzie[2] used to deride the spas because of their frequent exploitation and thought that about as much help could come by putting the salts in the bathtub at home, but while expressing his annoyance with the exaggerated commercialism of his day he did admit the favorable effect of these bath resorts as vacation centers with pleasant and relaxing music and beautiful scenery for those patients who were not too ill. As a minor but definite factor the hydrotherapy itself must be taken into consideration— the myriad little bubbles of the CO_2 baths can relax the patient and reduce the blood pressure for the time being.

Physiotherapy of other types at these bath resorts or at home can be another weapon favoring relaxation; massage and osteopathy undoubtedly can act thus but probably the best of such measures is mild exercise itself, unhurried and enjoyed, something that distracts the mind like fishing, or bathing, or exploring fields and forests on foot or horseback. A regular program can be fruitfully laid out for the mildly or moderately hypertensive person. If such an individual can be made to see the value of such relaxation early in his or her hypertension it is quite possible that the evolution of the disease can be altered, although it is as yet difficult to speak with certainty because of the lack of well controlled studies along this line. On the other hand, many of the games that nervous hypertensives seem to like to play such as cards are overstimulating and probably wisely omitted. Many of these seemingly minor details of life are very probably important to consider in the overall planning of the hypertensive's life.

For this life planning I would like to digress a moment and advise the institution of preventive medical measures for the young hyperreactors as well as for the obvious hypertensives, for it is from that group that the true hypertensives of the future spring. It is probably not going too far to give similar advice to the children of hypertensive parents, especially if both parents are hypertensive.

I have spoken of exercise and play and relaxation and physiotherapy but not of rest per se. It is, however, obvious that sedation and sleep are important since in our hypertensive work-up studies we often obtain absolutely normal blood pressure readings during deep sleep (from amytal) in severely hypertensive patients. There is a limit of time, of course, to pre-

scribe for bed rest each night and even in the day, but it should be possible to advise nine or ten hours in bed every night, with rare exceptions, and an hour's rest in the middle of the day before or after luncheon. If sleep evades the patient at times a hypnotic medicine will usually help.

Diet I shall discuss shortly but there are a few habits to be mentioned briefly first. Smoking tobacco usually constricts the peripheral arterioles, cools the skin, and sends the blood pressure up, even as much as 20 millimeters or more. Since that generally happens and since it seems rather silly to maintain a higher pressure throughout the day and evening by smoking a cigarette or even a cigar every hour or oftener, I advise my hypertensive patients to omit tobacco for good; half way measures are usually inadequate, but on occasion I have carried out pressor tests with tobacco in some of my more obstinate habituées and in rare cases there does seem to be very little or no effect.

Coffee and tea can be similarly tested if one wishes, though as a rule they seem to have no harmful effect, and the same is true of alcohol except in excess; as a matter of fact alcoholic drinks may have a favorable or sedative effect, but care should be taken that they do not put weight on these hypertensive patients who so often are inclined to be heavy anyway.

I may have seemed to have spent an undue amount of time this afternoon on the old and recognized measures of therapy such as Osler himself discussed, but I have done so intentionally for two reasons. In the first place, it is quite possible that some hyperreactors may be kept from becoming hypertensives by early heed to these things, and secondly, in the course of the current interest in radical measures of treatment, surgical and dietetic, there can easily be a neglect of these simpler measures, which though perhaps not curative can be helpful in adding their usefulness to the overall treatment, especially when the radical measures may have failed as they sometimes do, or may have been only partially successful.

Now for the rest of the time I shall speak of four measures which are at present creating a good deal of interest in this country but often in rather limited areas geographically or medically. The first of these is psychotherapy. My good friend Carl Binger of New York City has been one of the most active explorers in this field and wrote me only a few days ago that he has little to add to an article published in 1945 [3] in the New York Academy of Medicine Bulletin. He states that "the therapeutic results look promising, but it is too early to say." He had been associated with a group who carried on an intensive study [4] of the personality of 24 hypertensive patients, who showed from early life, before hypertension developed, an acute and chronic "failure of the integrative functions of personality which seemed to result from the inefficiency of the patterns of defense against anxiety and the weakness of the repressive mechanisms." One wonders how many persons with similar personalities do not have hypertension and if some hypertensives are exceptions to this pattern.

In 1945 Binger [3] wrote:

"The problem is that of treating a severe character neurosis in which anxiety, depression and suppressed aggression are the cardinal psychopathological features. The method of choice will vary from cheerful neglect (based on that much vaunted common sense which we are all supposed to possess in such good measure) to deep psychological exploration. The latter you will grant is a matter for the expert. What is to be hoped from it we cannot say. There is as yet no evidence that psychoanalysis or any other psychotherapeutic procedure can reverse the physiological process or change the destiny of this disease—be it benign or malignant. The problem is an open one. It needs further investigation. The ground has now been cleared for such an undertaking. It is probable that we can do more by way of prevention than cure.

"There is evidence that a correlation exists between levels of pressure and emotional disturbance and that suitable psychotherapy can ameliorate some symptoms: such as headache, fatigue, palpitation, dizziness, shortness of breath and the fear which these engender." . . .

"Leaving now out of consideration all efforts at deeper psychodynamic inquiry and turning to the every day handling of these patients, I believe that our new knowledge can be put to effective use. We are dealing with tender vessels. They need to be protected from emotional strain, especially from demands upon a self-reliance they do not possess. There is no good in telling them to 'buck up' and 'forget it.' They need the maximum of reassurance about the disease itself. They need very much to feel that some one person is watching over them and will take on his shoulders the burdens of their worries. They need to be encouraged to express their aggression, not by hurling dishes or epithets at their wives, but by directed work and play and by physical exercise, if this is compatible with their cardiac reserve. They need to be weaned away from an over-concern with the level of their blood pressure. The experienced doctor will vary his methods. With some he will be frank, with others he will be silent and to some he will have to dissemble. The manner in which this frightening fact is first presented to them is of the utmost significance. If the doctor shows his own alarm when the mercury column tops 220 it is likely to be communicated at once to his patients.

"It is well to remember that almost all our therapy is in essence psychotherapy. Drugs and sedatives, rest and exercise, diet and baths all have psychotherapeutic implications; and this is just as true of surgery. The surgical amphitheatre has become the court of last resort in this illness. Perhaps in time we will learn on what findings nature bases her verdict—why some patients respond to sympathectomy with a reduction in blood pressure, a recession of retinitis and a merciful relief from headache, while others do not. I hope that it will not be thought too 'tender-minded' of me if I suggest that the attitude which patients bring to the ordeal of operation may in some measure determine its effect upon them. For there are those who face it as they would doom and there are others who look upon it as a deliverance."

Next let us consider in order diets and medicines, both of which have been used in the treatment of hypertension ever since it was first discovered and indeed even before it was discovered per se. The first and obvious and as a matter of fact one of the most useful of all the diets has been that of low caloric value for the simple reduction of weight. It has long been known that the reduction of weight and the reduction of blood pressure in obese hypertensive patients often go hand in hand, and as an effective and helpful, though infrequently curative, measure a reduction diet stands high. Next

in point of origin, I believe, comes a low protein diet. It was quite natural to think that if the kidneys were damaged or under strain they should be spared extra effort of getting rid of excessive nitrogenous waste. However, such diets, although common and often spontaneously adopted by the layman who avoided red meat, were not strictly followed as a rule and on two counts were sometimes combated: (1) a man may live on meat and fat and nothing else for years and remain well, free of kidney disease and hypertension, and (2) if albumin is being lost freely in the urine in a case of hypertension extra protein may be helpful in counteracting such loss. Then came the early trial of a low salt diet for hypertension by Allen [5] and his colleagues, generally ignored by the profession at large. And now during the past few years there has been a revival of the interest of the dietary treatment of hypertension, with strict quantitative limitation of salt and protein.

To give you the latest news from several centers where such diets are being studied I shall quote with permission of the senders from telegrams received but a few days ago. Tinsley Harrison [6] with whom Dr. Grollman is associated at Dallas, Texas, wrote as follows: "Drastic sodium restriction of little or no value in severe hypertensives or in older patients. Will lower blood pressure in many young subjects and to normal level in some. Restriction must be so drastic that diet is rather impractical except for experimental use. Apparently the rice diet acts by virtue of low sodium content." Selye [7] wired from Montreal as follows: "Thus far dietary treatment only in animals. Clinical work limited to ammonium chloride therapy. We have found increased sodium to chloride ratios in some hypertensives analogous to hypochloremic alkalosis of Cushing's disease. In all patients with such an increase and in some with normal ratios such treatment has been of benefit. Paper about to be published." He has been treating his younger hypertensive patients for several months according to the following plan:

"1. a low salt diet (no extra salt in cooking or at table).
2. a low protein diet (only one helping of meat, fish or fowl or 1 egg per day, plus ordinary intake of vegetable protein). Caloric intake is amplified by carbohydrate as indicated.
3. 6 gm. of ammonium chloride per day in doses of 1½ gm. t.i.d. p.c. and at bedtime."

From Cleveland Corcoran and Taylor,[8] working with Page, wrote me as follows: "In our experience no specific effect of rice. Correction of obesity definitely effective. Correction of nitrogen and sodium retentions where renal status indicates very desirable."

Because of the considerable experience during the past four or five years of Dr. Kempner of Duke University at Durham, North Carolina, in the treatment of hypertensive patients with a strict rice diet and because of his reported success in a good many cases I myself made a pilgrimage to his clinic a month ago, saw some of his cases, and had a sample rice meal at one of

the rice houses in town. Kempner [9] introduced this diet some seven or eight years ago in the treatment of patients with renal disease and insufficiency because of both low protein and low sodium content and of the easily assimilated protein in the rice itself. The diet consists of rice, white or brown, boiled carefully for 20 minutes, served hot and relatively dry, 8 ounces or thereabouts a day in three courses with fresh or frozen fruits of nearly all kinds, and sugar more or less ad lib, to bring the total calories to 2,000 or a bit more. Between meals one may munch on rice-brittle candy. No meat, vegetables, milk, or salt is allowed for the first six weeks or so and then the diet may be gradually liberalized with two potatoes and a few ounces of meat weekly. Later if the blood pressure stays down one-third of the fruit is replaced by vegetables and more meat is given. There are only 20 grams of protein and far less than a gram of salt in this initial diet daily, and yet in many patients such limitation after they become accustomed to it and if they are willing to stick it out does not seem to cause any particular hardship, and light or even average work can be resumed without trouble. It is reported that about two-thirds of those hypertensive patients who are willing to give this diet a fair trial are distinctly helped by it subjectively and in blood pressure levels, and in some cases cardiac enlargement and eyeground abnormalities decrease or clear away and the electrocardiogram improves. Thus hypertensive heart disease has been proved to be reversible by the rice diet as well as by lumbodorsal sympathectomy.

I might add that I found the one meal on the diet that I took myself quite palatable and that I believe I would be willing to stick it out for a long time, with liberalization when circumstances permitted, provided it made me feel better and provided my blood pressure were significantly reduced thereby. I saw cases who had achieved a normal blood pressure by this therapy who had failed by other procedures, and it seems fair to me to suggest to some individuals, especially to those who are obviously unsuited for surgery, to try this diet; in fact it is quite reasonable to try this first for if it proves unsuccessful it is still possible to operate. Although the diet is difficult to take, surgery may be even more so. At the same time, of course, the measures that I have outlined at the beginning of the paper may be carried out concurrently and may appreciably help the dietetic effect.

Now let us turn to drug therapy. The obvious medicines and the ones that have been used most for many years are the sedatives and the nitrites. Bromides, but especially the barbitals, have been given and in particular phenobarbital, not only to induce sleep at night but also as rations through the day and with effect. We cannot, of course, maintain sedation heavy enough in most cases to keep the blood pressure of hypertensive patients at a normal level but even the smaller doses that are feasible, e.g. ¼ to ½ grain of phenobarbital three or four times a day, do help some, and this is a disease that needs attack from various directions in default of a specific cure as yet. The opiates except in crises should be avoided. Papaverine as an antispasmodic has been disappointing.

The nitrites do lower the pressure but as a rule too transiently or mildly in hypertension to make them worth while, and effective doses are likely to give headaches. The slowly acting mannitol hexanitrate has resumed some degree of popularity but we must await further proof of its effectiveness before accepting it for routine use.

The drug that has been periodically most popular during the past 20 years and which does lower the blood pressure somewhat in some cases is thiocyanate of potassium. It is, however, often disappointing and can in the more effective dosage be quite toxic. Also now that blood levels can be measured it should not be given without such occasional check.

Many other medicines for hypertension in the past have come and gone. Some have depended on the enthusiasm of some individual or countryside, some have been traditional, and some have helped certain complications or side-effects of the hypertension. None has been widely and permanently adopted although perhaps some should be subjected to more careful and critical pharmacological testing. Included among these drugs are garlic, pumpkin seed, watermelon seed, sunflower seed, mistletoe, veratrum viride, potassium iodide, theobromine and theophylline, benzyl benzoate, renal and other tissue or organ extracts, vitamins, and endocrine preparations, including the sex hormones.

Finally, we come to the newest of the drugs being tried in hypertension today, including tetraethyl ammonium salts and priscol. These chemicals have a physiologically sympathectomizing effect and eventually one may be found that will bring the blood pressure down to normal for a long enough period without important and disturbing by-effects to be introduced for routine periodic use. As yet nothing adequate has been found and the testing must still be regarded as in the experimental stage although many workers are hot on the trail.

Last but not least among the therapeutic procedures for hypertension is the surgical measure of sympathectomy. Other surgery such as renal decortication and unilateral nephrectomy has not relieved essential hypertension itself. Nor has irradiation of the adrenal glands, although spectacular relief has been achieved on occasion by excision of a pheochromocytoma. Introduced by Rowntree and Adson [10] over 20 years ago sympathectomy has slowly evolved from its disappointing early status to its present effective position, largely because of Smithwick's introduction [11] over seven years ago of the more extensive procedure of lumbodorsal sympathectomy which has been worthwhile in two-thirds to three-quarters of the patients operated on by Smithwick, or more so still in the younger cases with high diastolic and low pulse pressures and good renal function. It has been life-saving in a considerable number of my patients who had already developed hypertensive heart disease, and a few years ago established more than had any other experience my realization of the not infrequent reversibility of heart disease. Uncommonly hypertensive patients will spontaneously lose their hypertension in the course of years, but my observation of cases subjected to lumbo-

dorsal sympathectomy or perhaps to the rice diet too has been a new experience in the past few years. It is to be hoped that something easier than either the lumbodorsal sympathectomy (or the rice diet) may be found in the near future to control the devastating effect of hypertension which still remains in this country and in the world at large one of the chief causes of disability and death.

I have finished this brief review of the management of hypertension. It is obvious that we still have a long way to go and a lot to do before we shall have achieved our goal. Meanwhile we should avail ourselves of all the measures that have been proved worth while from the simple but important planning of the way of life in early cases or in preventive medicine to the more radical and lifesaving measures in serious cases whose days are otherwise numbered.

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ATYPICAL FACE PAIN; A STATISTICAL CONSIDERATION OF 66 CASES *

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HEADACHE and pain in the face are two difficult problems with which the practitioner of medicine must reckon. Unusual and irregular facial pain seems almost more of a therapeutic chore than the more familiar distress of headache.

REVIEW OF THE LITERATURE AND CONSIDERATION OF TERMINOLOGY

Glaser [1, 2, 3] reviewed the problem with painstaking care in 1928, in 1938 and again in 1940. In 1928, 143 case histories from the Hospital of the University of Pennsylvania were studied critically and the complete syndrome of atypical face pain was presented for the first time and was called "atypical facial neuralgia." The records were analyzed from the standpoint of age at onset of symptoms, sex incidence, side involved, number of operations performed for relief, events coincident with the onset of distress, distribution and type of pain, agents used for the relief of pain, factors aggravating the pain and associated phenomena referable to the sympathetic nervous system. The author referred to the patients afflicted with this ailment as a pathetic lot and emphasized that no matter what course of treatment was pursued, the ultimate results were the same—dismal failure. In 1938, Glaser and Beerman [2] completely reviewed the literature to that date and cited the pioneer work of Sluder [4] and Cushing [5] and referred to the earlier reports of Fay,[6, 7] Davis and Pollock,[8] Wilson [9] and others. They presented 57 new cases which were added to their original 143. It was pointed out that Frazier and Russell [10] in 1924 had first used the term "atypical neuralgia" only for want of a better one. At the conclusion of this communication by Glaser and Beerman in 1938 it was stated:

"The term atypical neuralgia is not satisfactory but has been used to describe a peculiar, deep seated, aching pain that is not constant, not paroxysmal or intermittent, but marked by attacks of greater or less severity, occurring at varying intervals. Remissions are rare. Associated with this pain are sympathetic phenomena in 50 per cent of the cases. The pain does not follow the distribution of any of the cranial nerves and involves the scalp as well as the face." This, then, is the clinical problem to be considered in this report.

In 1940, Glaser [3] pointed out that significant additions had been made in

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the preceding 10 years to the knowledge of the sensory nerve supply of the face and progress has been made in the classification of the various clinical entities which could produce atypical face pain. In this review, while he still urged extreme caution in the carrying out of therapeutic measures, the note of pessimism sounded in the discourse in 1928 ("We have been absolutely nonplussed in our attempts to account for the origin of the pain phenomenon or to provide a remedy of any kind") had given way to a brighter note ("The pain need no longer be looked upon as incurable"). This transition to a more optimistic attitude regarding treatment and prognosis was, for the most part, due to his careful separation of the "secondary atypical neuralgias," the "neuralgias due to systemic diseases," and "neuralgias due to lesions of the head, chest and abdomen" from "primary atypical neuralgia." Glaser specifically referred to a group of cases which Brickner and Riley [11] designated as "autonomic faciocephalalgia" and cited three cases in which pain had been relieved when the patient received ergotamine tartrate and epinephrine. The striking component of the seizures which were relieved was the presence of symptoms definitely referable to the autonomic nervous system. Brickner and Riley quoted extensively from the publication of Vallery-Radot and Blamoutier [12] who described a case in which this component was present. They suggested that neither the term "atypical neuralgia" nor the term "atypical migraine" was proper and proposed the new term "autonomic faciocephalalgia," not for the purpose of applying a new term to an old syndrome, but as a means of getting away from old terms and conceptions which they felt to be misleading. Fay,[13] too, emphasized the need for thinking of these atypical neuralgias as either vascular neuralgias or definite nerve problems.

The thought was advanced by Glaser and Beerman in 1938 that all patients who have atypical facial pain should be given a trial of treatment with the various vasoconstrictor and vasodilator drugs. By this trial it might be possible to determine whether or not certain conditions might be removed from the perplexing group of primary atypical neuralgia. Such a course has been pursued at the Mayo Clinic in the section in which this study was made since 1936 in all cases of atypical facial pain.

Recent publications on this subject have been presented by Schreier,[14] Reichert,[15] Hyslop,[16] Martin,[17] Horton,[18] Gittins [19] and Walker.[20] The majority of these authors reviewed the literature and suggested certain medical or surgical procedures that have been attempted for relief of the pain. These procedures included division of the facial artery, vein and the accompanying sympathetic nerves,[15] blocking of the cervicothoracic portion of the chain of sympathetic nerves [15] and resection of the sphenopalatine ganglion.[17] They also referred to the now almost abandoned procedures of cervical sympathectomy and the stripping of the sympathetic plexus from the carotid trunk. Walker [20] questioned whether relief might not someday be offered some of these patients by prefrontal leukotomy.

No further consideration of the literature will be undertaken nor will the method of production of the pain be reviewed. Specialists in the field of neurophysiology, neurology and neurosurgery have described the method of production of pain in meticulous detail. Suffice it to say that the exact means of the conduction of pain in the obscure neuralgias of the head and face is a matter of some doubt. However, impressive evidence that multiple pathways may transmit such distress and that the vasculature, both arterial and venous, plays a significant rôle has been presented. Fay [7, 13] emphasized the rôle of the vasculature, and Davis and Pollock [8] studied particularly the part played by the sympathetic nervous system.

Study of 66 Cases

Our report will be concerned only with a statistical analysis of the case histories and a consideration of the therapeutic measures attempted in our section at the Mayo Clinic. Our primary purpose is to re-present the syndrome of atypical face pain and the records of 66 patients encountered in the section from January, 1940, to December, 1945, inclusive, have been analyzed carefully with this aim in mind. Four cases illustrative of the syndrome will be reported.

Incidence. Approximately 5,100 patients have been examined in the section in the course of six years. Sixty-six (1.29 per cent) of these were referred from the various general and special sections of the Mayo Clinic with a diagnosis of atypical face pain. The patients presented ailments which were not amenable to the more usual forms of treatment. The number of the patients studied in each of the years included in this review is as follows: 1940, six patients; 1941, twelve patients; 1942, thirteen patients; 1943, nine patients; 1944, eight patients; 1945, eighteen patients. Forty-six women and 20 men were observed. The distribution by sex is essentially the same as that in previous reports.

Table I

Age Distribution at the Time of Admission and of Onset of Pain

Age	On Admission*			At Onset		
	Men	Women	Total	Men†	Women‡	Total
0 to 19	0	0	0	1	6	7
20 to 29	1	9	10	4	14	18
30 to 39	9	14	23	8	10	18
40 to 49	4	14	18	5	13	18
50 to 59	4	8	12	0	1	1
60 to 69	1	1	2	2	1	3
70 and above	1	0	1	0	0	0
Average	43.3	39.6	40.7	35.9	33.0	33.3

* Youngest patient was 24 years old; oldest, 70 years old.
† Youngest man was 20 years old; oldest, 68.
‡ Youngest woman was 17 years old; oldest, 61.

Age. The age of patients at the time of their admission to the clinic, by decades, is given in table 1. The average age of the men at onset of symptoms was 35.9 years and of the women, 33.0 years. The man who was youngest at the time of onset was 20 years old and the oldest was 68 years old. The woman who was youngest at the onset of symptoms was 17 years old and the oldest, 61 years old. The average age at onset for both sexes was 33.3 years. Additional data are presented in table 1. Data concerning duration of symptoms are given in table 2.

TABLE II

Duration of Pain

Years	Men	Women
0–1	6	8
2–3	2	7
4–5	4	13
6–10	3	11
11–15	3	1
16–20	1	5
21–30	1	0
31–40	0	1
Average, years	7.07	6.84
Shortest, months	7	2
Longest, years	27	35

Occupations. Five of the men were farmers, there were one each of the following: janitor, salesman, outdoor guide, lawyer, jeweler, optician, insurance agent, newspaper man, auto salesman, hotel manager, bartender, clerk, doctor and broker (investment and finance) and one was unemployed. The occupations of the women were as follows: Thirty-four were housewives; four, teachers and three, clerks. There was one each of the following: tax investigator, barmaid, registered nurse and beautician and one had no occupation.

Marital Status and Information Concerning Families. Sixteen of the 20 men were married and four, unmarried. Of the 46 women, 34 were married, one was divorced, three were widowed and eight had not married. Four of the married women had married for the second time and one of the widows had been married twice. Of the total group of 51 married patients 13 had no children. The problems of sterility, of sterility after the birth of one child and of one partner wanting a child or more children while the other did not seemed to occur more often than might be expected in such a small series. One patient had had an illegitimate child and an imbecile was born to one patient.

Miscellaneous Information. Neither the nativity of the patients nor their residence at the time of onset of the pain was considered to be of any significance. A careful review of the family histories revealed no significant information. None were stated to be relatives of the insane. No family history of trigeminal neuralgia or atypical face pain was given by any of the patients. No significant disease of the nervous system was present in the families of these patients according to the patients' records. A normal

complement of tuberculosis, diabetes, cancer and allergic disease was noted. One woman stated that one of her parents had had "a bleeding disease." No notation of a convulsive disorder in a relative was made in the records. Only a few references to migraine headache in the family histories were noted.

Medical and Surgical Histories. Medical histories were reviewed. Four patients had had gonorrhea and one had had syphilis which seemed of significant concern to him. One patient had had bronchiectasis. Two patients had suffered Bell's palsy in the year of onset on the side of the face subsequently plagued with pain.

An analysis of the surgical histories revealed the following data: Twenty patients had undergone appendectomy; five had undergone herniorrhaphy; four, cholecystectomy; four hemorrhoidectomy, and one each, thyroidectomy, gastric resection and transurethral prostatic resection. Two women had undergone perineal repair; six, hysterectomy; four, bilateral salpingectomy; five, unilateral oöphorectomy and two, bilateral oöphorectomy. The menstrual function had been halted in seven patients by these procedures but only two of the women had been castrated.

Twenty-three patients had undergone significant operations on the nose and paranasal sinuses. Tonsillectomy had been performed in 38 cases. The records do not state clearly in how many cases tonsils or adenoids or both had been removed for the relief of the facial pain, but such a procedure certainly had been carried out for this purpose in the majority of the cases. Although it was not recorded the vast majority of the patients had undergone

TABLE III

Previous Neurosurgical Procedures

Procedures	Men*	Women†
Alcohol injection of the fifth cranial nerve	7‡	10
Procaine injection of the fifth cranial nerve	1	7§
Section of the fifth cranial nerve	1	6
"Pinching of the fifth cranial nerve"	1	
Pre-auricular block		1
Craniotomy. Gasserian neurectomy?	1	
Section of the infra-orbital and supra-orbital nerves	1	

[Note: Information was obtained from patients; hence, the neurosurgical terms are not precise. Operations on the fifth cranial nerve involved a peripheral branch in the majority of instances.]

* Six men underwent 12 operations.
† Eighteen women underwent 24 operations.
‡ One patient had three injections.
§ One patient received three injections.

some dental operation in the course of their quest for relief of pain. In 36 cases attempts had been made to interrupt the pathways by which the pain was conducted (table 3). Fourteen of the 20 men and 28 of the 46 women had not undergone neurosurgical procedures.

Weight. The average weight of the men was 167 pounds (75.7 kg.). The maximal weight was 250 pounds (113.4 kg.) and the minimal weight, 119 pounds (54.0 kg.). The highest recorded weight of the women was

173 pounds (78.5 kg.) and the lowest, 101 pounds (45.8 kg.). The average was 132 pounds (59.9 kg.). Gross obesity or significant maldevelopment or malnutrition did not occur.

Use of Alcohol and Tobacco. The use of alcohol by these patients was noted. Only one case of near alcoholism was encountered. On a grading scale of 1 to 4 in which 1 represents the least and 4 the greatest consumption, the intake of the alcohol by three men was considered to be consumption, grade 1; three men, consumption, grade 2; five men, consumption, grade 3, and nine abstained from the use of alcohol. Thirty women stated that they were abstainers; consumption of alcohol by 15 women was graded 1 and for one woman consumption was graded 3. Applying the same scale to use of nicotine the results for men were as follows: no tobacco, four; grade 1, two; grade 2, eight; grade 3, five, and grade 4, one. The results for women re-

TABLE IV

Events Coincidental with or Related to (?) Onset of the Condition*

Coincident Conditions or Related Events†	Men	Women
Dental operation	1	5
Sinusitis	3	1
Trauma		
Automobile accident	1	
Football accident	1	
Struck by jaialai ball	1	
Blow in face by husband		1
Operation on sinus	2	3
Influenza		3
Tonsillectomy		1
Vincent's angina	1	
Removal of cyst of jaw		1
Alcohol injection		1
Exposure during a snow storm		1
Thyroidectomy		1
Diagnosis of carcinoma of rectum		1

* Information obtained from the patients' records.
† Ten men and 27 women stated that the pain was of spontaneous origin.

vealed that 28 did not smoke; consumption by seven was graded 1; of seven, graded 2, and of four, graded 3.

Blood Pressure. Study of determinations of blood pressure showed the average systolic blood pressure for the men was 124 mm. of mercury; the highest was 152 mm. and the lowest, 100 mm. of mercury. The average systolic blood pressure for the women was also 124 mm. of mercury; the highest was 170 mm. and the lowest, 95 mm. The average diastolic pressure for the men was 79.5 mm. with a high of 110 mm. and a low of 60 mm. and for the women the average diastolic pressure was 81.0 mm. with a high of 100 mm. and a low of 68 mm. Neither hypertension nor hypotension was a significant feature in these cases.

Physical Examination. The general physical examination of these patients was notably nonrevealing. A multitude of minor conditions, as would be found in any group of patients of similar age, was discovered. Five

women were definitely experiencing the menopausal syndrome and were receiving or recently had received treatment with estrogenic substances. No major physical aberration was noted in the group.

Special Examinations and Laboratory Studies. It may be stated at this point that in almost every case, special examinations were conducted by laryngologists, ophthalmologists, otorhinolaryngologists, neurologists and dental specialists at the clinic as part of the routine study of this condition. In the event that the patient had undergone previous neurosurgical procedures, the residual areas of anesthesia were noted and similarly, the evidence of previous dental operations or operations on the sinuses could always be seen. The rhinologists occasionally noted minor septal defects or thickening of the sinus membranes but on no occasion did they consider that significant disease of the nose or throat was present. On the few occasions that an electro-encephalogram was made, negative results were reported. Similarly, results of roentgenologic examination of the head, the face and other special structures were consistently negative and of no significance.

TABLE V

Side of the Face Involved

	Left Side	Right Side	Both Sides	Alternating Sides
Men	11	6	2	1
Women	23	21	0	2
Total	34	27	2	3

Studies of blood chemistry, sedimentation rate, basal metabolic rate and urinalysis revealed no significant findings.

The average concentration of hemoglobin for the men was 14.7 gm. per 100 c.c. and for the women, 12.9 gm. The lowest recorded value for any patient was 11.0 gm. The patient was a woman. Significant anemia was not detected. The average leukocyte count for men was 9,000 and for women, 7,000. In two cases in which the patients were men, leukocytes numbered more than 9,000; in one, 12,500, and in another, 16,200. These high counts appeared to be of no significance. The flocculation test for syphilis gave negative results in all cases.

Information Concerning the Pain. Table 4 shows the events and conditions which patients felt were related to, or coincidental with, the onset of facial pain. The only events or conditions mentioned by more than one patient were infection of or operation on the paranasal sinuses, dental operation, trauma and postinfluenzal distress.

The only significant fact gained from consideration of the side of the face affected (table 5) is that our cases differ from those so conscientiously reviewed by Glaser. He pointed out that the involvement of the left side, the right side and both sides of the face occurs in essentially the same number of cases.

Table 6 shows the wide and irregular distribution of the pain. Apparently it is not distributed along established nerve pathways. It is readily seen that an explanation for such distribution of pain on a vascular basis

TABLE VI

Location and Distribution of the Pain

Type of Distribution			Cases*
Individual region		Cheek (zygomatic region)	7
		Upper jaw (overlying ramus of mandible)	4
		Lower jaw (overlying body of mandible)	1
		Maxilla	1
		Infra-orbital region	1
		Total	14
Centered in cheek with distribution to one other region		Eye	2
		Nose	2
		Upper jaw	1
		Pre-auricular region	1
		Post-auricular region	1
		Total	7
Centered in cheek with distribution to two other regions		Supra-orbital region. Neck	1
		Eye. Temple	2
		Nose. Infra-orbital region	2
		Nose. Teeth	1
		Auricular region. Lower jaw	1
		Total	7
Centered in cheek with distribution to three other regions		Nose. Maxillary region. Upper jaw.	1
		Infra-orbital region. Eye. Temporal region.	1
		Nose. Temporal region. Auricular region.	1
		Temporal region. Supra-auricular region. Postauricular region	1
		Total	4
Centered in jaw with distribution to one other region	Upper jaw	Maxillary region	2
		Temporal region	1
		Frontal region	1
	Lower jaw	Chest	1
		Vertex of skull	1
		Total	6
Centered in jaw with distribution to two other regions		Occiput. Tragus of the ear	1
		Nose. Inside of mouth	1
		Infra-orbital region. Supra-orbital region	1
		Base of nose. Infra-orbital region	1
		Maxillary region. Supra-orbital region.	1
		Pre-auricular region. Infra-orbital region	1
		Maxillary region. Temporal region	1
		Total	7
Centered in jaw with distribution to three other regions		Cheek. Neck. Shoulder	1

* Total cases, 46.

TABLE VII

Duration of the Attacks of Pain

Duration of Pain	Men	Women
1 to 60 minutes	6	4
1 to 24 hours	5	5
1 to 7 days	4	8
Almost constant	1	5
Constant	3	20*
Data not available	1	4

* One patient in this group obtained relief by taking codeine.

might be more consistent with the findings than an explanation on a neurogenic basis.

Of the terms used by the patients in description of the distress the word "dull" was used 15 times; the word "ache" was also used 15 times. The specific expression "like a toothache" was used four times. The sense of "deep pain" was described by several patients and the impression was gathered in reviewing the records that this sensation was common to more than just several patients. A sense of "constancy" was attributed to the pain by nine patients. Sixteen described a pain component in addition to the more constant, dull ache. This additional element of distress consisted of occasional "sharp twinges" or "jabs" of pain. The word "severe" was used by eight patients and "excruciating" by four. Several patients at-

TABLE VIII

Factors Which Relieved the Pain*

Factor	Men†	Women
Heat	8	9
Cold		4
Moist cold		1
Warm dry climate		1
Summer	1	
Rest	3	
Diversion of interest		1
Pressure on eye	1	
Pressure on area of pain	1	
Pressure on great vessels of neck		2
Pressure on facial artery		1
Acetylsalicylic acid	3	7
Ephedrine	1	
Codeine		5
Morphine		3
Alcohol (by mouth)		3
Pentobarbital sodium		2
Atropine (intravenous)		1
Nicotinic acid		1
Preparation containing menthol		1
Hypodermic injection (probably not an opiate)	1	
Pregnancy		1
Swimming		1
Any neurologic procedure		1
Crying		1
Gum chewing		2
Data not available		9

* Information taken from the history.
† Temporary remission for no apparent reason in seven cases.

tempted to describe a sense of weight or of pressure in the region where the pain occurred and several described the pain as "burning." Some of the more unusual descriptive words and phrases were: "an aching kind of numbness," "a severe, hard ache—a blank feeling," "like sharp files boring through the skin," "a burning pain associated with an alum and salty taste" and "a

TABLE IX

Factors Which Accentuated the Pain*

Factor	Men	Women
Heat		2
Cold	2	13
Cold drink		1
Dampness	1	1
Dry air	1	
Winter	3	1
Summer		1
Weather change	1	
Temperature change		1
Wind		1
Light		2
Sneezing	1	2
Coughing	1	1
Yawning		1
Crying		1
Facial movement		2
Wrinkling nose	1	
Washing face	1	2
Shaving	1	
Brushing teeth		1
Blowing nose		1
Exercise or effort	2	
Stooping		1
Standing		1
Lying down	1	
Sudden jolts of body	1	
Being awake	1	
Being asleep	1	
Weight of glasses		1
Local pressure	1	
Alcohol (by mouth)	3	4
Chocolate		1
Eggs		1
Milk		1
Menstruation		1
Nervousness	1	14
Fatigue		6
Time (midnight to 8 a.m.)		1
Almost everything		1
Nothing	1	
Data not available	4	13

* Information taken from the history.

smooth pain with throbbing." Perhaps, as typical a descriptive phrase as any was "a dull, severe ache—unbearably throbbing at times."

In table 7 the duration of the attacks of pain is given. Twenty-three patients complained of constant pain and six of almost constant pain or a total of 29 patients with essentially constant distress. Twelve patients measured their attacks by days, 10 by hours and 10 by minutes. It will be observed that the duration of individual episodes of distress of the women seemed significantly longer than of the men.

The factors which offered relief to these patients are given in table 8. It will be noted that eight women had resorted to taking opiates whereas according to the records none of the men had. The multiplicity of measures offering relief to the women is also of interest.

Patients stated that numerous factors accentuated their facial distress (table 9). Again the multiplicity of measures mentioned by the women is

TABLE X

Vascular Element

	Men	Women	Total
Present	5	11	16
Probably present	4	8	12
Probably absent	6	5	11
Absent	5	22	27
Total	20	46	66

impressive. Also, the obvious fact that emotional stress and nervous tension played significant rôles was recognized by 14 women and by none of the men.

We attempted to evaluate whether or not a vascular element was present in the distress of the individual patient (table 10). This is a highly personalized analysis and, as such, has a minimum of objective value. Such factors as the opinions of consultants who studied the patients, response to vasoconstricting and vasodilating drugs and the presence or absence of such phenomena of the sympathetic nervous system as lacrimation, rhinorrhea, hidrosis, hyperemia of the skin or conjunctiva, alterations in the size of the pupil and prominence of the blood vessels were considered.

TABLE XI

Results of Treatment*

Relief	Men	Women	Total
Complete	1	2	3
Significant	2	4	6
Moderate	3	7	10
Slight	3	3	6
No relief	9	25	34

* No treatment was given to seven patients (two men and five women).

The presence or absence of the so-called functional factor in the background of these patients certainly deserves consideration. Of the 20 men, seven had a significant functional background for their complaint of pain in the face. Terms used by various consultants to describe these patients or their condition were "hypersensitive," "large functional element," "chronic nervous exhaustion," "neurogenic" and "psychogenic."

An element of psychoneurosis was thought to be present in 30 of the 46 cases in which the patients were women. The grading system in which 1

represents a mild and 4 a severe condition was used. Results were: grade 1, five patients; grade 2, fourteen; grade 3, eight; grade 4, three. Some of the terms used by the various consultants to describe the condition of these women included "functional," "early paranoic," "highly emotional," "unstable," "much tension" and "chronic nervous exhaustion." Whether or not such functional features preceded the pain in the face and were responsible for the production of pain in some measure or whether such features followed the long period of unrelieved pain is not known. It is barely possible that we have sought refuge in the comparative medical security of a diagnosis of functional disease when some obscure organic problem—vascular, neurogenic or otherwise—has escaped our attention.

Differential Diagnosis. The conditions most commonly considered in the differential diagnosis were: the major neuralgias of the head, face and neck; Paget's disease; Costen's temporomandibular syndrome; Sluder's sphenopalatine neuralgia; calculus in the submaxillary duct; disease of the nasolacrimal duct and diseases of the teeth and paranasal sinuses. A diagnosis of trigeminal neuralgia was not made in any case in this series. A section of the sensory root of the fifth cranial nerve was performed on one occasion and did relieve an associated paroxysmal, sharp component of the patient's distress but did not relieve the dull, throbbing ache which was the chief complaint. The "trigger-like" factors mentioned in table 9 were not particularly constant nor did they provoke a neuralgia-like pain. They were not the true trigger mechanisms noted in trigeminal neuralgia.

TABLE XII

Treatment Which Gave Relief

Degree of Relief	Therapeutic Agents	Men	Women
Slight	Histamine (intravenously)	2	
	Histamine desensitization	1	2
	PT 9		1
Moderate	Histamine (intravenously)		1
	Histamine desensitization	2	2
	Histamine desensitization and benadryl (intravenously and orally)		1
	Histamine desensitization and thyroid extract		1
	PT 9	1	
	D.H.E. 45 and saline		1
	Atropine (intravenously)		1
Significant	Histamine desensitization	2	1
	Histamine (intravenously), nicotinic acid, benadryl		1
	Histamine (intravenously), nicotinic acid; thyroid extract; adrenalin		1
	Adrenalin		1
Complete	Histamine desensitization		1
	Histamine desensitization, Kendall's cortical extract, nicotinic acid (intravenously)	1	
	Histamine desensitization, Kendall's cortical extract, PT 11		1

TABLE XIII

Therapeutic Agents Employed at the Clinic

A. Histamine and histamine-like agents
   1. Histamine diphosphate (Abbott Laboratories)
   2. Hapamine (histamine-azoprotein, Parke, Davis & Company)
   3. The "PT" drugs (The Maltbie Chemical Company)
      PT–8 β(2-pyridyl) ethyldiethylamine hydrochloride
      PT–9 β(2-pyridyl) ethylmethylamine hydrochloride
      PT–10 1, (2-pyridyl) 2, (methylaminopropane) hydrochloride
      PT–11 β (2-pyridyl) ethylamine hydrochloride
B. Antihistamine agents
   1. Benadryl (β dimethylaminoethyl benzhydryl ether hydrochloride, Parke, Davis & Company)
   2. Pyribenzamine hydrochloride (N′-pyridyl-N′-benzyl-N-dimethyl-ethylene diamine hydrochloride, Ciba Pharmaceutical Products, Inc.)
   3. Torantil (histaminase, Winthrop Chemical Company, Inc.)
C. Hormones
   1. Estrogenic substance
   2. Androgenic substance
   3. Thyroid
   4. Kendall's adrenocortical extract
D. Vitamins
   1. Vitamin A
   2. Vitamin C
   3. Vitamin B complex
   4. Nicotinic acid
   5. Thiamine
   6. Vitamin P
E. Chemotherapeutic agents
   1. Sulfonamides
   2. Penicillin
F. Anesthetic agents
   1. Procaine hydrochloride
   2. Alcohol
   3. Trichlorethylene
G. Analgesic agents
   1. Acetylsalicylic acid
   2. Sodium salicylate
H. Hypnotics and sedatives
   1. Barbiturates
   2. Dilantin sodium (diphenylhydantoin sodium)
I. Parasympathetic agents
   1. Mecholyl chloride (acetyl-β-methylcholine chloride)
J. Parasympathetic depressants
   1. Atropine
   2. Tincture of belladonna
K. Vasoconstrictor drugs
   1. Adrenalin
   2. Gynergen (ergotamine tartrate, Sandoz Chemical Works, Inc.)
   3. D.H.E. 45 (dihydroergotamine methanesulfonate, Sandoz Chemical Works, Inc.)
   4. Oxygen
L. Miscellaneous agents
   1. Roentgen therapy
   2. Rosenow's vaccine
   3. Specific vaccine
M. Placebo therapy

Treatment. Results of treatment in the section determined at the time the patient was dismissed are given in table 11. Three of the patients said that their pain had disappeared completely. In two of these three cases results of the "provocative test" in which histamine is injected subcutaneously were positive. The therapeutic agents used in the cases in which

some relief was obtained are listed in table 12. A complete listing of the therapeutic measures which we used is made in table 13.

Case Reports

Case 1. A married housewife, 26 years old, first came to the Mayo Clinic in March, 1945, with a complaint of pain in the right side of the upper jaw and right side of the lower jaw of eight years' duration. The pain apparently began spontaneously and then continued intermittently for the eight years preceding admission. Nine months before she was examined at the clinic the pain began to occur more frequently and to be more severe. Two months later she had all of her upper teeth removed. The pain was described as a constant aching soreness and burning, with occasional throbbing, of the right side of the upper jaw and right side of the lower jaw with occasional extension to the occiput and the tragus of the right ear. The pain sometimes felt like a "cold needle." A sharp, shooting, electric-shock component which lasted for only a few minutes accompanied the pain and occurred infrequently. The patient felt that, in some manner, this sharp pain was related to bowling, lifting and such exertional activity.

Many diagnoses had been made prior to admission of the patient to the clinic and these included trigeminal neuralgia, brain tumor, "cancer," "a maladjusted mandible" and dislocated vertebra of the neck. Many types of operation had been suggested.

The patient had been reared in a boarding home. Her parents had separated when she was four years old. She had had her tonsils removed in 1930. She had had pneumonia in 1920 and again in 1943. She related in a psychiatric interview that she had memories of an unhappy early childhood and that she frequently had been beaten severely by her father. She complained bitterly of the lack of parental affection. Her marriage had not been entirely happy. Sexual relations had never been satisfactory and the patient stated that she had a vigorous sexual appetite which was rarely satisfied. The patient had left her children for someone else to care for and had come to Rochester to live and to work until she received relief from the pain.

Physical examination revealed that the patient was an asthenic, weak and weary appearing woman of rather high intelligence. A papular eruption of indeterminate character was observed over the dorsum and the skin was described as "greasy." Results of general physical examination and routine laboratory studies were negative. No abnormalities were revealed on roentgenologic examination of the head, cervical portion of the spinal column and thorax. Study of the eyes, including funduscopic examination, study of the perimetric fields and refraction, special examination in the section on neurology, special examination of the ears, nose, throat and larynx and dental examination were made and all gave negative results.

The patient was treated in our section with various "vascular drugs" for six weeks. The following observations were made: 1. The intravenous administration of adrenalin invariably decreased the pain in the face but did not obliterate it completely. 2. The intravenous administration of histamine invariably made the pain worse. 3. When 150 to 200 mg. of benadryl [21] was given daily prior to the administration of histamine the customary response of pain to histamine did not occur.

By treatment with benadryl and histamine diphosphate we were able to keep the patient free of pain for 12 days. Our apparent success was terminated when the patient's husband came to visit her. When the patient was dismissed from our care the diagnosis was atypical face pain with definite vasodilating feature and a marked psychogenic element. The patient obtained no further relief from our therapeutic efforts.

Case 2. A woman, 44 years old, was examined in our section in February,

1942. Her complaint was of pain of two years' duration in the right side of the face. The family history was noncontributory. Marital history indicated that the patient was married for the first time in 1918 and was divorced after 11 years of marriage. In 1937 she married again. Past medical and surgical history revealed that the patient had undergone bilateral salpingectomy and tonsillectomy and had had typhoid fever, scarlet fever and influenza as a child.

The pain apparently had developed after the patient had had some teeth filled. In a subsequent attempt to relieve this pain, her dentist extracted two third molars and replaced all of her fillings. The pain was described by the patient as a severe ache not unlike that of a toothache which extended from the right side of her lower lip into the right side of her lower jaw and into the anterior part of the ear (not the canal). No trigger mechanisms were present. The inside of the mouth was not involved. The patient had had excellent medical care prior to her admission at the clinic. Procaine hydrochloride and alcohol had been injected in the sensory root of the right fifth cranial nerve on two occasions without relief. She also had received much medical treatment, including administration of estrogenic substance, large amounts of supplementary vitamins and calcium by mouth, heavy sedation and analgesia.

Physical examination revealed that the patient was a well-developed, well-nourished white woman whose face was slightly asymmetrical. The left orbital fissure was narrowed slightly. Her teeth contained many fillings. Some slight tenderness over the right temporal artery was present. Examination of the thorax, abdomen and pelvis, laboratory examination, including study of the urine and blood, roentgenologic examination of the head and thorax, examinations in the sections on otolaryngology, neurology, gynecology and dental surgery, examination of the eyes, including refraction, perimetric field study and funduscopy, and an electro-encephalogram were made and results were negative. Roentgenologic study of the cervical portion of the spinal column revealed localized hypertrophic changes in the fifth and sixth cervical vertebrae. The basal metabolic rate was normal. The ophthalmologist explained that the narrowing of the orbital fissure resulted from structural changes in the eyelids.

The patient was studied several times in the section, the last time in 1945. The ultimate result was total therapeutic failure. The patient, however, did contend that during three weeks in 1945 when benadryl was administered by mouth and histamine diphosphate by the intravenous route, she enjoyed the only period of freedom from pain which she had known since the onset. Unfortunately, this relief could not be maintained. No significant amelioration or exacerbation of the distress was obtained consistently with the use of either vasoconstricting or vasodilating drugs. The diagnosis when the patient was dismissed from the clinic was atypical face pain without vasodilating features. A marked functional element was thought to be present.

Case 3. A married woman, 51 years old, was admitted at the clinic in 1941. Her chief complaint was of pain in the left side of the face of three years' duration. The pain apparently followed the removal of a "small cyst of the jaw" by a dental surgeon. The patient had not been free of the pain since its onset.

A sister had migraine headaches. The patient had been married for 20 years, had had four miscarriages and one living child. The past medical history was not unusual. The patient had undergone right oöphorectomy. Subsequently laparotomy had been performed for intestinal obstruction. Operation on the right maxillary sinus had been performed some years previously. The patient related that some polyps had been removed.

The pain was described as a constant, dull, pulsating, drawing ache with a "burning and seething" quality in the left cheek bone with occasional paroxysms of

sharp, shooting pain spreading into the forehead and into the neck. The pain often occurred at night. This pain had become worse gradually. The paroxysms were brought on by chewing, talking and rubbing the face. Nothing had ever completely relieved the pain. Cold seemed to help slightly but the application of heat made the pain definitely worse.

Physical examination and complete laboratory studies of the blood and urine gave completely negative results. Roentgenologic examination of the head, cervical portion of the spinal column and thorax revealed no abnormalities. All of the physicians who examined the patient at the clinic doubted that she had trigeminal neuralgia. Subsequently this patient was admitted to the clinic eight times. Later in 1941 a deep injection of the sensory root of the fifth cranial nerve with alcohol was performed for diagnostic purposes and the patient gained significant relief. In 1942 the pain recurred and division of the posterior sensory root was suggested as a final resort for relief only of the sharp neuralgic pain. The patient chose to undergo this operation. The sharp pain was relieved, but the patient returned later with the same constant dull aching distress which had been her chief complaint prior to the neurologic operation. This patient was the only one in the series to undergo a neurosurgical operation other than local block for diagnostic purposes. In October, 1945, the patient returned contending that the pain was worse than it had ever been. On physical examination, a large, wide, elevated red streak in the skin was observed. The streak covered the middle portion of the left cheek and was definitely warm to the touch. The patient stated that this colored area perfectly indicated the region in which she suffered pain. The colored area was apparently present only when the pain was unusually severe. She had long complained of this color change, but it had never been observed at the clinic. The surface temperature of the red area in the left cheek was 32.9° C. (about 91° F.) and of the right cheek, 29.7° C. (about 85° F.), in a room in which the temperature was 25.6° C. (78° F.) and the humidity 40 per cent. This was checked several times and each time the left cheek definitely was 3° C. warmer than the right. Some lacrimation of the left eye and plugging of the left nostril was noted.

Intravenous administration of adrenalin did not eradicate the pain but did cause some of the redness to disappear. Intravenous administration of benadryl seemed to offer some relief of the pain in the cheek but this was certainly not complete. On a subsequent occasion the intravenous administration of benadryl when the redness was present seemed to offer approximately 80 per cent relief of pain. The patient contended that benadryl offered the most significant relief she had ever obtained.

The patient remained relatively pain-free for four months and then returned to the clinic with the same complaint after having failed to take the prescribed medication in any regular fashion. Treatment with histamine diphosphate (desensitization) [22, 23] and benadryl offered significant relief. Recently administration of pyribenzamine has kept this patient more comfortable than any previous medication.

Case 4. A woman, 40 years old, registered at the clinic in August, 1944. Her chief complaint was of intermittent pain in the left side of the face of two years' duration. The pain apparently began, after a severe attack of "flu," in the left side of the lower jaw and proceeded toward the vertex. The patient stated that she had refrained from going out at night into the cool air because if she did so the pain invariably developed. Occasionally this same distress occurred in the right cheek.

The past history and the family history were totally unrevealing. Complete laboratory studies of the blood and urine, including serologic tests, gave negative results. The provisional diagnosis was sphenopalatine ganglion neuralgia. The left middle turbinate (concha nasalis media) was enlarged and almost blocked the air passage. It was removed at the clinic. The patient obtained no relief from this operation.

Later it was possible for us to produce the facial distress by exposing the patient to the cold draft of an electric fan. Histamine desensitization was attempted for a long period but the attempt was not successful. The diagnosis when the patient was dismissed from the clinic the last time was atypical facial pain with a marked psychogenic element.

Comment

Certain comments and interesting sidelights which have appeared in the literature regarding this troublesome syndrome are most deserving of repetition. Wilson [9] concluded that in some cases the condition was definitely psychogenic in origin and was based on deep, irreconcilable conflicts. He stated that "the face has become almost synonymous with the personality, . . . therefore, it is no wonder that shocks to the pride, long suppressed regrets and difficulties recognized but not allowed to reach the surface would cause a functional disturbance of this unit that could become a chronic source of irritation."

Fay,[13] as well as Glaser,[1, 2, 3] emphasized that every effort should be made to eliminate the secondary factors which may bring about the pain and that in those cases in which the pain has been present for a short time only, the results of treatment are far better than those in which the pain has persisted for a long time. Fay [13] also reëmphasized the critical point that extreme caution must be observed in carrying out operative procedures on such structures as the teeth, the sinuses and the nervous system unless a pathologic process is definitely known to exist in these regions. Unwarranted assault on these structures almost invariably makes the patient's suffering more intense.

The need for a complete study of these patients with careful examination of all the special sense organs, roentgenologic study of the skull and careful neurologic and psychiatric study has been emphasized by Walker.[20]

Gittins,[19] in a paper concerning periodic headache and neuralgia with or without associated vasomotor symptoms, stated that, "Actually, just getting older accounts for the largest group of so-called 'cures,' regardless of whether or not there has been any treatment or even a diagnosis." He suggested that the reduction in the number of prospective victims is probably more a social than a medical problem.

Fay [13] pointed out that the three main difficulties in clarification of this problem are: (1) the variation in nomenclature, (2) the difficulty the patient has in describing his distress and (3) the variety of reports in the literature of small series of cases with varied treatment and poor or no follow-up data.

The general consensus in the literature seems to be that this syndrome is a manifestation of some structural or physiologic disturbance of the sympathetic nervous system which is either primary or secondary to some focal pathologic condition or is a manifestation of an underlying pain mechanism of the vascular system which may be distinct from the sympathetic nervous system.

Summary

We have submitted a brief review of the literature relevant to the syndrome of atypical facial neuralgia known by many other names in the literature and designated at the Mayo Clinic as atypical face pain. This term is preferred because it seems the most descriptive and, in the absence of specific knowledge as to the etiology of this condition, also seems most accurate. Interest has been manifest in this subject since the early contributions of Sluder (1908–1918).

We have attempted to re-present the syndrome as first described by Frazier and then completely described by Glaser. A statistical analysis of 66 consecutive cases encountered in six years has been presented.

The ratio of women to men was approximately 2:1. Similar ratios have been noted in other reports. The average age of patients at the onset of the pain was 33.3 years and the average duration was seven years.

The occupations of the patients were of no medical significance. A study of the marital status was of little assistance except to reveal 13 of the married patients were childless. The nativity, place of residence, family history and past medical history were of little note. No significant problems of obesity, underweight, hypertension, hypotension, alcoholism, major physical defects, anemia or leukocytosis were encountered in this series. Special laboratory studies of blood chemistry, urinalysis, roentgenologic studies, electro-encephalography and determinations of the basal metabolic rate were not enlightening.

The left side of the face was involved slightly more often than the right which was probably of no statistical significance. The distribution of the distress was widespread on the affected side. The descriptive terms used by the patients were mentioned and the concept that the sensation was a deep, dull, almost constant ache, often throbbing, was obtained. Twenty-eight patients had essentially constant distress. A significant number of dental operations, operations on the nose and paranasal sinuses and needless neurologic surgical procedures had been performed. A wide variety of agents and medications improvised by the patients or suggested by physicians elsewhere provided some relief and a similarly wide variety of factors accentuated the distress. Women stated that some 20 factors offered relief. They ranged from chewing gum, through pressure over the great vessels of the neck and face, to the use of opiates. Eight patients had at least some degree of addiction to the opiates.

Twenty-eight patients presented symptoms, in addition to the pain, which were highly suggestive of the presence of a vascular factor. These comprise about 42 per cent of the patients studied, a figure in substantial agreement with that given by Glaser for a much larger series.

The condition of 30 of the 46 women (approximately 65 per cent) and of seven of the 20 men (35 per cent) was thought to have a significant functional element.

Only nine patients obtained any significant relief and but three of these were relieved completely. The procedures which offered such relief are tabulated. A total listing of the preparations and procedures attempted in our section is given. The impression was obtained that the patients who had the most significant degree of vascular symptoms (that is, phenomena associated with the sympathetic nervous system) were more likely to obtain relief with treatment such as histamine desensitization or the use of vasoconstrictor medications. For example, two patients who obtained complete relief had been proved to be sensitive to histamine and the symptom complex had been reproduced with this agent, a process entirely akin to the well-established syndrome of histaminic cephalalgia.

Study of this small series permits no conclusions. This communication serves only to reëmphasize the difficulties in diagnosis and treatment and to contribute information concerning the condition. We are in complete agreement with the authors of recent medical articles who suggest that some of these cases of atypical pain in the face may represent a basic vascular problem and that the patient who has pain of obscure origin in the face and head deserves a trial of medication with vasodilating and vasoconstricting agents. It is a defect of our presentation that follow-up data are absent. We did not think that the results of treatment of a condition which is so difficult of description could be evaluated properly from a study of questionnaires. Consequently we elected to utilize the dismissal note on the patient's record and the patient's estimate of relief to determine whether improvement had occurred. We are well aware that the tendency in conditions of this type is for any new or different medication to offer at least transitory relief. For this reason, we wish to reëmphasize that no claims are made for our therapeutic endeavors in this bizarre and mystifying problem. Certainly, any conservative management is deserving of trial and extended clinical study.

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STREPTOMYCIN IN THE TREATMENT OF TUBERCULOSIS IN HUMANS

I. MENINGITIS AND GENERALIZED HEMATOGENOUS TUBERCULOSIS *

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INTRODUCTION

SHORTLY after the first report on streptomycin by Waksman and his associates,[1] Feldman and Hinshaw observed that the drug exerted a pronounced effect upon the course of tuberculous infections in guinea pigs.[2] On the basis of these findings, a clinical investigation was started, and in September 1945 Hinshaw and Feldman reported that streptomycin exerted a suppressive effect upon the course of various forms of tuberculous infections in humans.[3] Although the therapeutic claims of these investigators were notably restrained in this and their subsequent reports,[4, 5] it was apparent that the alterations in the course of tuberculous infections observed by them were completely unprecedented.

As a result of these findings, an investigation of streptomycin in the treatment of tuberculous infections was initiated on the Cornell-New York Hospital Medical Service in January 1946. The present report is based on the observation of 17 patients with meningeal, miliary or other forms of generalized hematogenous tuberculosis who were treated during the first 18 months of the study. The results in 43 patients with pulmonary tuberculosis treated with streptomycin during the same period, are reported separately.[6]

OUTLINE OF THE INVESTIGATION

Preparation of Streptomycin. A uniformly prepared and highly purified streptomycin sulfate was used. Its preparation and properties have been presented else-

* Portions of this study were presented before the annual meetings of: the American College of Physicians, April 29, 1947; the American Society for Clinical Investigation, May 5, 1947; and the Section on Internal Medicine of the American Medical Association, June 12, 1947.

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The first part of this investigation was conducted under the direction of the National Research Council Committee on Chemotherapeutics and Other Agents, Dr. Chester S. Keefer, Chairman. The subsequent investigation is a part of the Streptomycin Manufacturers-American Trudeau Society program which is being conducted in collaboration with the Tuberculosis Study Section of the National Institute of Health. The streptomycin was furnished by the Chemotherapeutic Committee; by a generous donation from Charles Pfizer and Company, Inc., Brooklyn; and from supplies donated to the American Trudeau Society by the Streptomycin Manufacturers.

The study was aided in part by grants from the National Institute of Health, and from the Lederle Laboratories, Inc., Pearl River, New York.

where.[7] The biologic potency of the final product coincided with the value for theoretically pure material, and is estimated to be at least 95 per cent pure. All of the material used was streptomycin A.[8, 9]

Streptomycin Regimen. A constant total daily dose of three grams of streptomycin administered intramuscularly in six or eight divided doses was used in all 12 of the adult patients. In the five children and infants, the dose was adjusted to body weight (20,000 micrograms per kilogram). In general, the total period of therapy was 120 days. Patients with meningitis received streptomycin intrathecally as well as by the intramuscular route. Individual doses of 0.1 to 0.375 gram (0.05 to 0.1 gram in infants) were administered at intervals ranging between 24 and 72 hours for total periods of 60 to 90 days. As evidence was soon obtained that individual doses of 0.2 to 0.375 gram were not always well tolerated,[7, 10] the 0.1 gram dose was not exceeded throughout the greater part of the investigation.

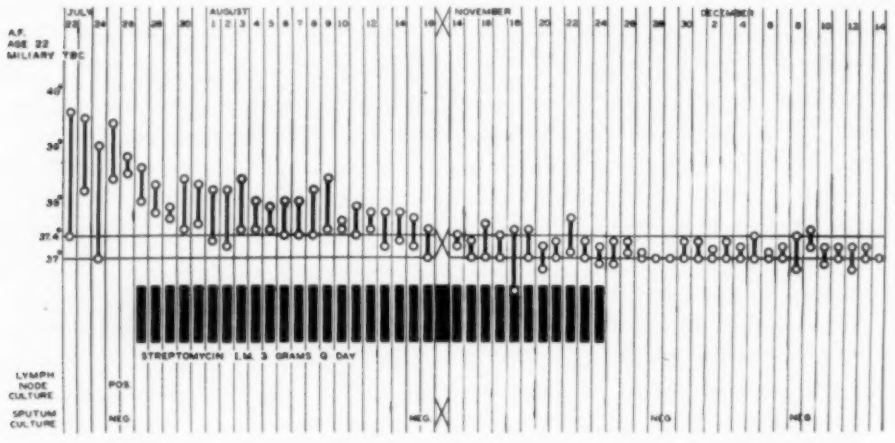

FIG. 1*a*. Patient A. Fo, generalized miliary tuberculosis. Temperature chart showing daily range in degrees centigrade.

Roentgenologic Studies. Standard stereoscopic posterior-anterior exposures were made on every patient before treatment and at two-week intervals during the four months thereafter. Subsequent films were obtained at intervals of approximately one month. Lateral views were made whenever necessary.

Skin Sensitivity to Tuberculo-protein. The skin sensitivity to tuberculo-protein was tested before streptomycin treatment and at monthly intervals thereafter by the intracutaneous injection of appropriate dilutions of old tuberculin.

Bacteriologic Studies. Specimens of sputum (or other purulent exudates) were concentrated, digested with sodium hydroxide, and cultured on both the Tween *-albumin medium of Dubos and Davis,[11] and egg-potato (Petragagni) medium, at two-week intervals during and subsequent to therapy. The particular Tween-albumin medium used contained 0.5 per cent albumin and 0.02 per cent Tween, and was incorporated into a solid medium with 1.5 per cent agar. When the presence of tubercle bacilli could not be demonstrated by culture of the sputum, gastric washings were obtained and similarly cultured. Pericardial, pleural, or cerebrospinal fluid and blood were cultured directly in the Tween-albumin liquid medium as well as on the Petragagni medium.

* "Tween 80" is the trade name of the polyoxyethylene derivative of sorbitan monooleate, furnished through the courtesy of the Atlas Powder Company, Wilmington, Delaware.

In Vitro Studies of Streptomycin Sensitivity. The tubercle bacilli isolated from the patients before and at intervals after the institution of streptomycin therapy were tested in vitro for sensitivity to streptomycin in the following manner.

Five c.c. of the liquid medium (Tween 0.02 per cent—albumin 0.5 per cent, pH 7.0) which contains 500 mcm. of streptomycin per c.c. were pipetted into the first two

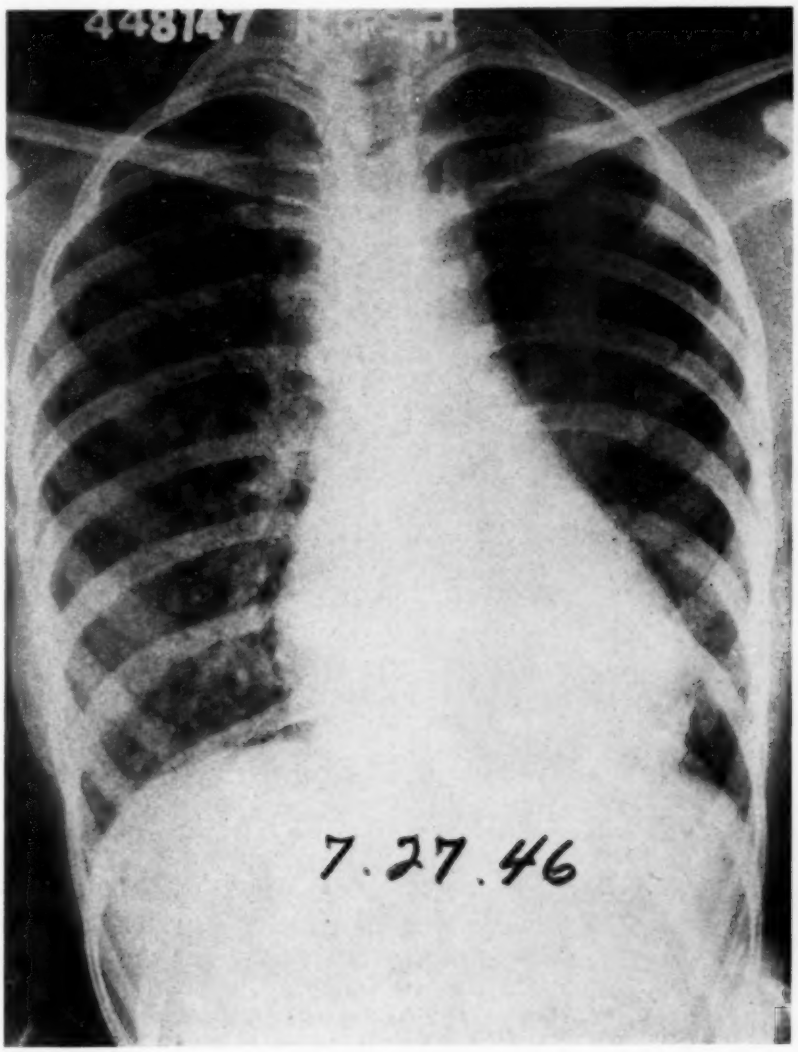

FIG. 1*b*. Patient A. Fo., chest roentgen-ray at start of streptomycin treatment. Note enlargement of cardiac shadow.

of a series of 10 tubes (six by one inch). An additional five c.c. of liquid medium were added to the second tube. Two-fold serial dilutions were then made, starting with the contents of the second tube and continuing throughout seven tubes. Thus, in the total of nine tubes the final concentrations of streptomycin ranged from 1.9 to 500 mcm. per c.c. Five c.c. of liquid medium which contained no streptomycin were

pipetted into the tenth tube which served as a control. The culture which was to be tested was grown for four to six days in the liquid Tween-albumin medium. The culture was first diluted with the liquid medium to a standard density, and 0.1 c.c. was inoculated into each of the 10 tubes. The cultures were incubated at 37° C., and were examined daily from the fourth to the seventh day after inoculation. The presence or

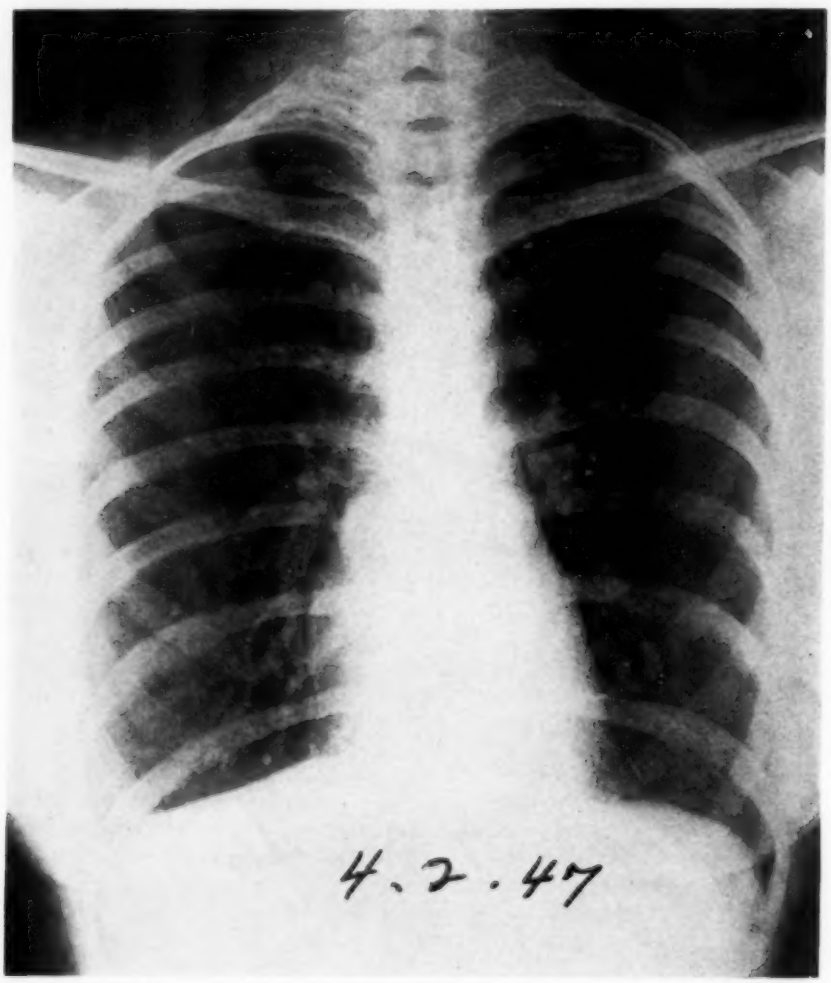

FIG. 1*c*. Patient A. Fo., chest roentgen-ray 8 months after start of 120 day course of streptomycin treatment. Note complete clearing of miliary infiltrations.

absence of growth was determined by gross inspection. The end-point was recorded in terms of the lowest concentration of streptomycin in which no growth was detectable on the seventh day of incubation. During the first half of the investigation, streptomycin concentrations higher and lower than the 500 to 1.9 mcm. per c.c. range were included in the test. It was found that no valuable information was obtained by the use of such concentrations, and that the test is more conveniently performed with the use of only ten tubes.

Pharmacologic Studies. The concentrations of streptomycin in the various body fluids and exudates were determined by the bioassay method of Stebbins and Robinson [12] and by the chemical technic of Boxer and Jelinek.[13] In order to investigate the toxicity of the highly purified streptomycin on long-continued administration, the function (and histopathologic changes) of a number of organs and systems were studied by appropriate technics. The results of these studies have been published elsewhere.[7, 10, 14]

Observations and Results

Tuberculous Meningitis. Nine patients with bacteriologically proved tuberculous meningitis have been treated with streptomycin. In seven, the meningitis arose as a complication of acute miliary tuberculosis and all seven have died. The remaining two, neither of whom had miliary tuberculosis, have been in remission for five months since the cessation of therapy.

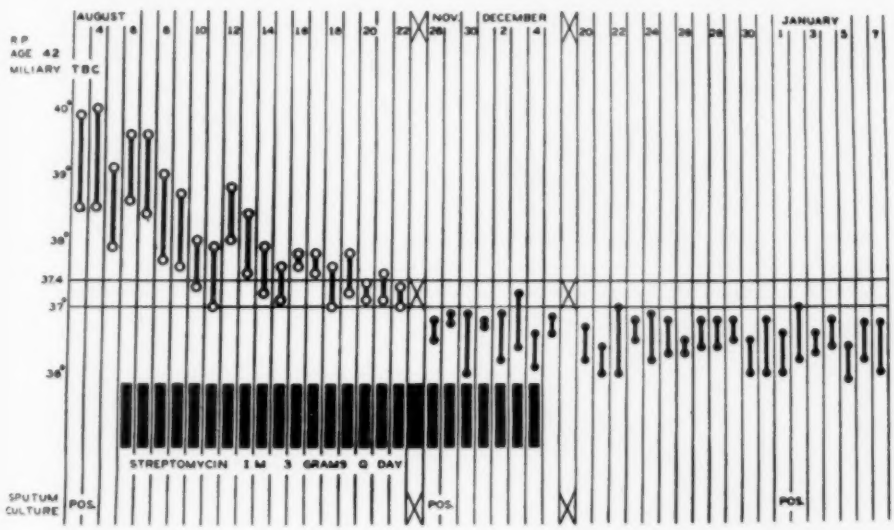

Fig. 2*a*. Patient R. Ph., generalized miliary tuberculosis which developed in course of chronic pulmonary tuberculosis. Temperature chart.

Only four of the nine patients presented the characteristic clinical picture of acute tuberculous meningitis at any time during the course of the infection. In the other five, all of whom have died, the meningitis ran a subacute or asymptomatic course in an illness which was dominated by the manifestations of acute miliary tuberculosis. The two types will be considered separately.

Clinically Evident Tuberculous Meningitis. At the time streptomycin therapy was started, all of the four patients with clinical meningitis were acutely ill with high fever and nuchal rigidity. One was in deep coma, another was stuporous, and the remaining two were irrational. Symptoms suggestive of meningitis had been present for one to four weeks before the institution of antimicrobial therapy.

The patient in coma, a two year old infant with previous miliary tuberculosis, never regained consciousness although she survived three and a half months after the start of therapy. Tubercle bacilli could not be cultured

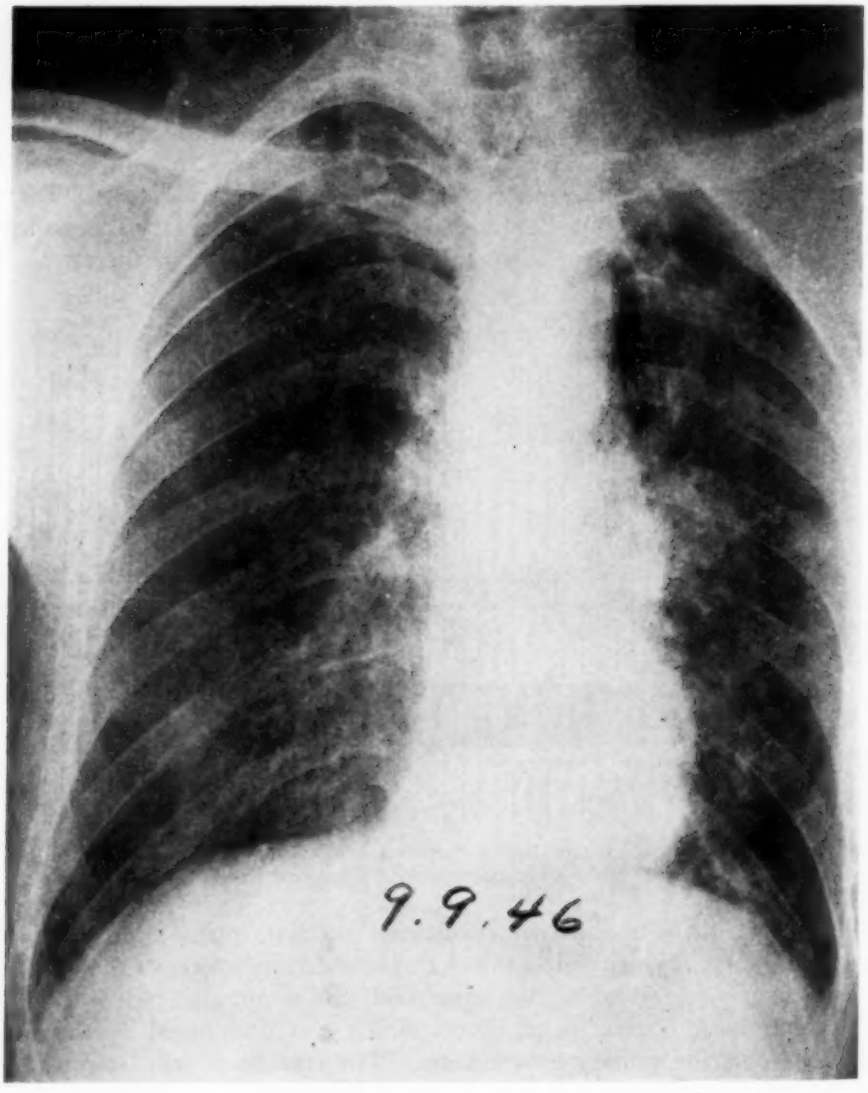

FIG. 2*b*. Patient R. Ph., chest roentgen-ray at start of streptomycin. Note left apical cavity unclosed by thoracoplasty which had been left incomplete because of ipsi-lateral bronchogenic spread. Disseminated hematogenous miliary infiltrations well seen in contra-lateral lung.

from the cerebrospinal fluid after the seventeenth day of therapy, and cultures of the brain and cerebrospinal fluid at autopsy were sterile. Death occurred as a consequence of internal hydrocephalus, and only a few tiny areas of

meningeal inflammation were demonstrable on microscopic examination of the tissues. Although it appeared that the streptomycin had exerted a considerable effect upon the course of the meningeal infection, the central

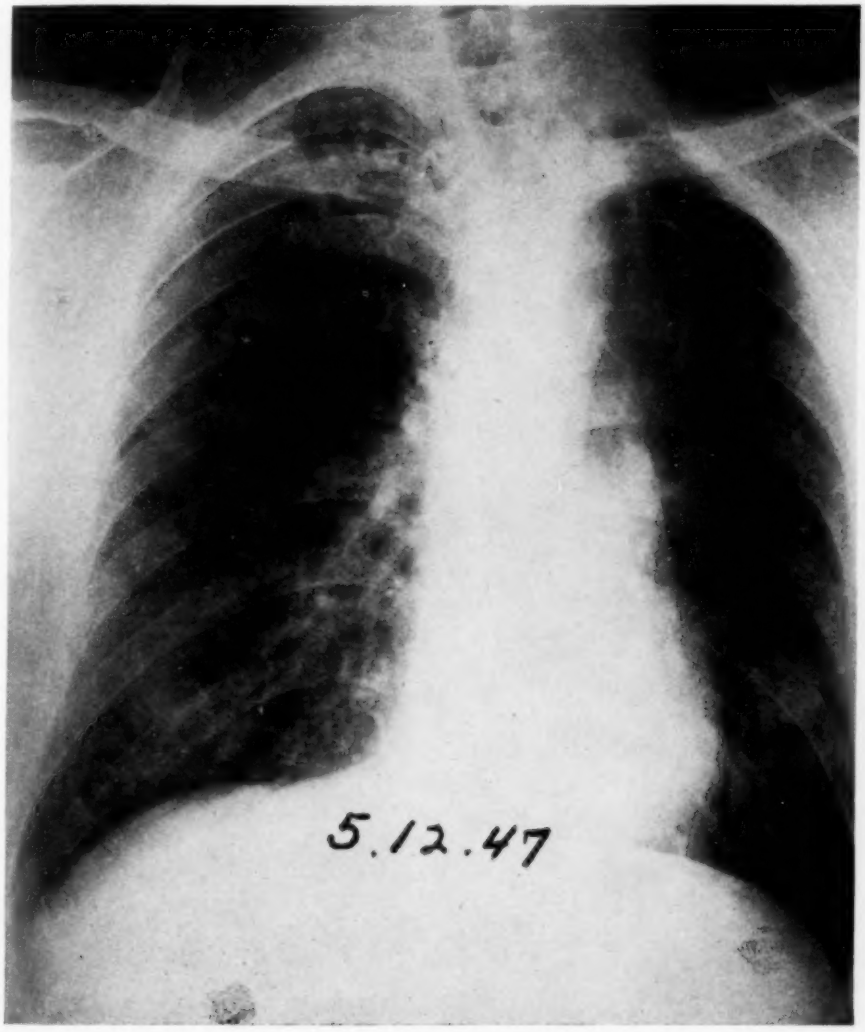

FIG. 2*c*. Patient R. Ph., chest roentgen-ray 9 months after start of 120 day course of streptomycin. Note closure of cavity, conspicuous regression of bronchogenic infiltrations, and disappearance of miliary infiltrations.

nervous system presumably had been damaged before treatment to an extent which precluded ultimate recovery.

The other patients with obvious meningitis included a 63 year old man with associated miliary tuberculosis and two 19 year old women with no evidence of generalized hematogenous dissemination. They showed con-

siderable improvement during the first seven to 10 days of streptomycin which was administered both intrathecally and intramuscularly.

Improvement consisted of a decline in fever within three to five days of the start of therapy and an appreciable decline in nuchal rigidity so that it

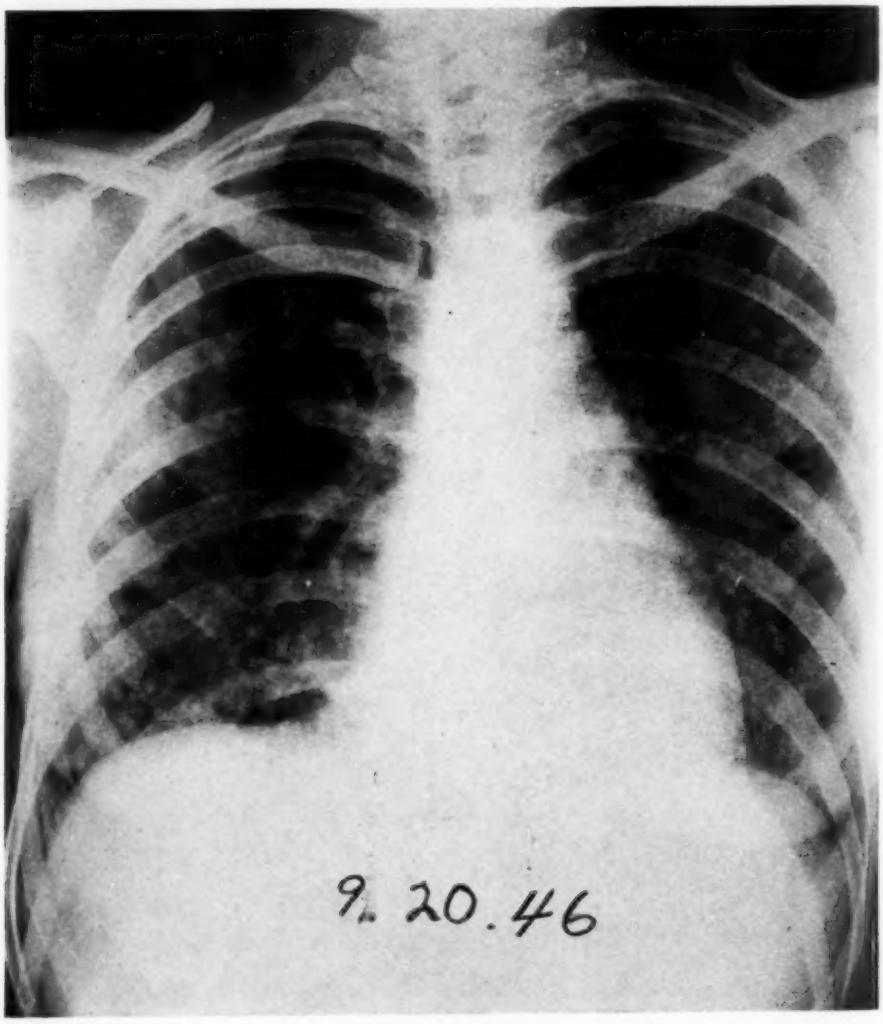

FIG. 3*a*. Patient R. Sc., case of acute generalized miliary tuberculosis transformed into chronic infection with residual activity in scattered foci. Chest roentgen-ray at start of treatment. Note relatively large size of "miliary" infiltrations.

was only barely detectable at the end of the first week. The two irrational patients became much more alert and the patient who had been stuporous regained consciousness. Subsequent to the first seven to 10 days of therapy daily variations in the status of the meningitis were no longer perceptible.

The patients presented the picture of a subacute or chronic illness. Fever (37 to 38.5° C.) continued, and the principal symptoms (headache, backache, leg pains) could be attributed with equal likelihood to either the disease or the intrathecally administered streptomycin.

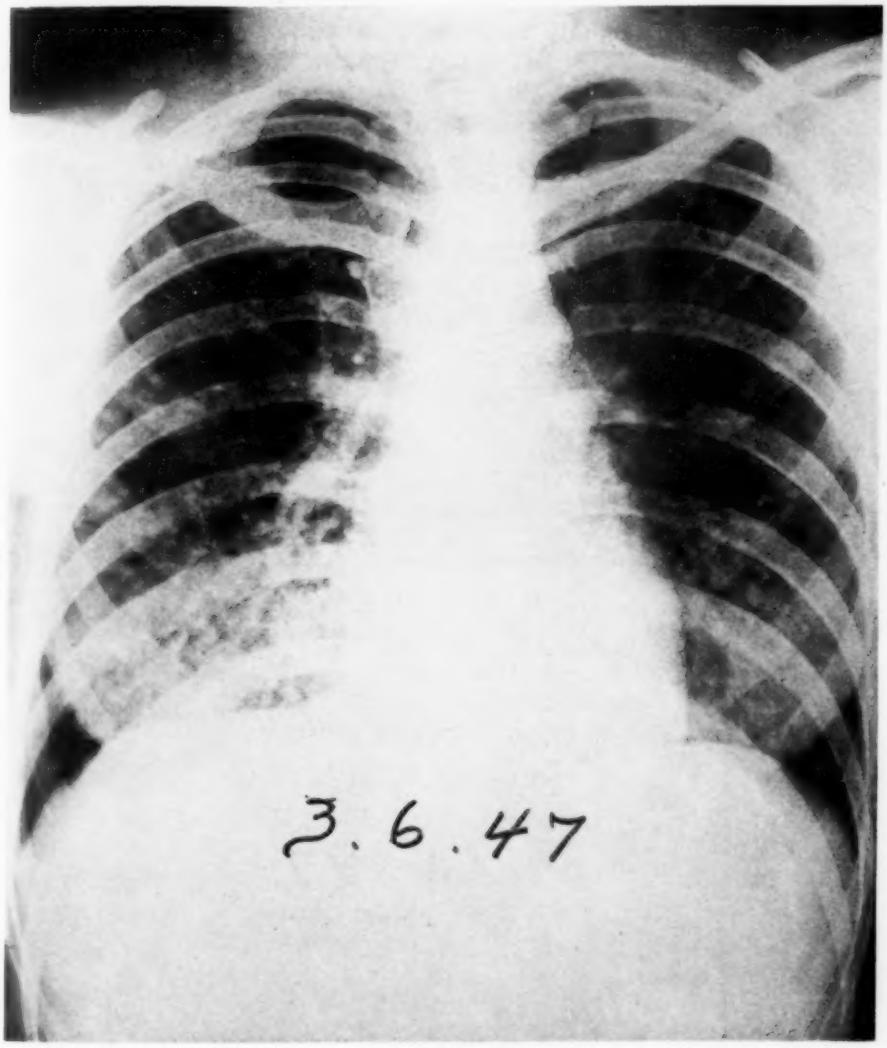

FIG. 3*b*. Patient R. Sc., five and one-half months after start of treatment.

The subacute illness, without appreciable daily change, persisted for approximately one month. The 63 year old man died suddenly on the thirty-ninth day of treatment. Postmortem examination revealed an extensive purulent meningitis involving the spinal cord, and minimal evidences of meningitis over the base of the brain.

The two young women, neither of whom had miliary tuberculosis, continued to present the same clinical picture of subacute illness during the second and the third months of treatment. Although they did not appear acutely or dangerously ill, there was no tangible indication that they would recover. During the fourth month of streptomycin therapy, when the

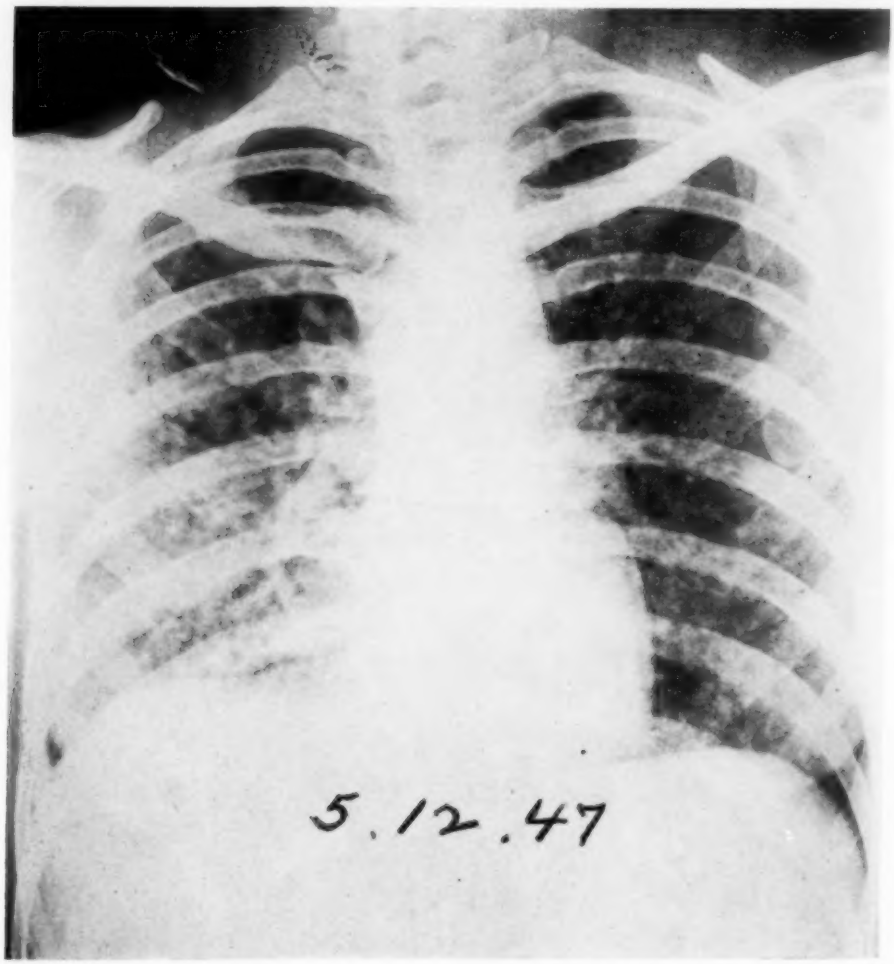

FIG. 3*c*. Patient R. Sc., nearly eight months after start of treatment. Except for a pleural haze in the right lower lung field, resulting from an intervening pleurisy, the picture is not appreciably changed.

intrathecal administration of the drug had been discontinued, improvement was apparent and the patients became virtually asymptomatic.

Five months after the cessation of streptomycin therapy, these two young women show no signs of meningitis, present no evidence of mental impairment, and have normal cerebrospinal fluids save for protein concentrations

of 68 and 75 mg. per cent. One patient has been totally deaf since the fifth week of therapy. This phenomenon may represent a sequel of the infection or may have resulted from streptomycin toxicity.[7, 10, 14] The other patient is under care for tuberculosis of the spine which was discovered after, but probably antedated, the onset of the meningitis.

Subacute or Asymptomatic Tuberculous Meningitis. Six of the nine patients had acute miliary tuberculosis but did not present the characteristic clinical picture of meningitis at the time streptomycin therapy was started. One of them was the infant already described, whose clinically characteristic meningitis occurred as a late relapse of a previous meningeal infection. In one of the six the cerebrospinal fluid was not examined prior to therapy.

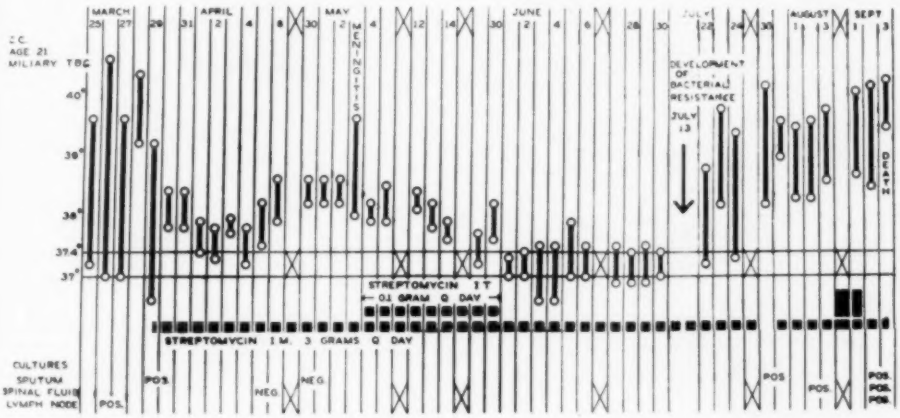

FIG. 4*a*. Patient C. Co., generalized miliary tuberculosis illustrating diphasic course with relapse despite uninterrupted treatment. Temperature course. Note recurrence of fever after development of bacterial resistance.

In only two of the others was the pre-treatment cerebrospinal fluid shown to be abnormal. Both received streptomycin intrathecally as well as intramuscularly at the start of antimicrobial therapy. The remaining four patients received no streptomycin intrathecally until meningeal involvement became evident. It should be noted that this complication did not appear until after 35 to 96 days of streptomycin therapy.

The first indication of meningeal disease was a relatively sudden increase or return of fever at a time when the miliary tuberculosis appeared to be receding under therapy. The rise in temperature was accompanied by slight headache but all other clinical evidences of neurologic disease were lacking. Cerebrospinal fluid examinations revealed characteristic abnormalities of meningitis.

The addition of intrathecally administered streptomycin to the therapeutic regimen was usually followed by reduction in fever and disappearance of headache. During the first month of intrathecal therapy, the clinical course was essentially the same as that observed in the same period in the patients

with frank clinical meningitis. Two attained temporary remissions of the meningitis. One of them remained completely well physically and mentally for a six week period during which she received no antimicrobial therapy. Her remission was followed, however, by clinically evident and eventually fatal meningitis. It is worthy of note that in this group, hers was the

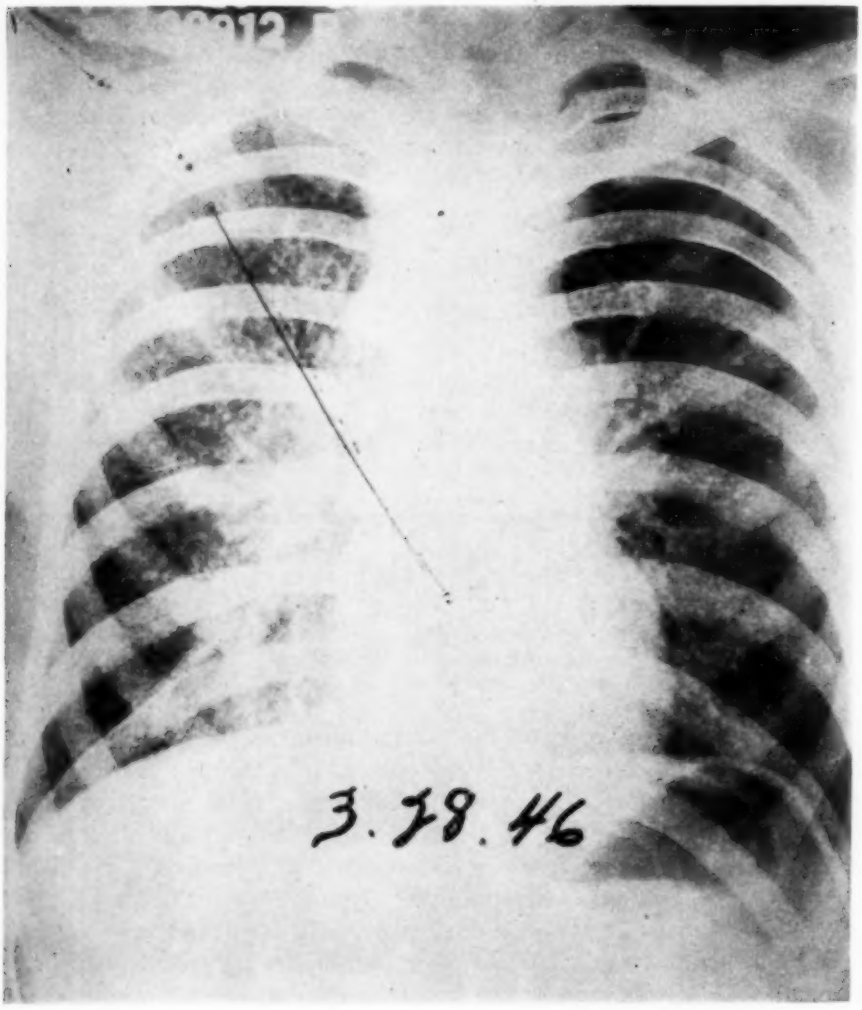

FIG. 4*b*. Patient C. Co., roentgen-ray of chest before start of streptomycin treatment.

only death which was clearly attributable to meningitis. The second patient remained free of clinical evidence of meningitis but an increased cerebrospinal fluid protein persisted for a period of three months after the cessation of the intrathecally administered streptomycin. Death in this instance, as well as in the other patients of the group, apparently resulted from relapsing strepto-

mycin-resistant generalized hematogenous tuberculosis and not as a consequence of meningitis. In all the fatalities, however, bacteriologic evidence of the persistence of the meningitis was present at death.

The duration of life from the first evidence of meningitis to death or relapse ranged from 20 to 124 days in this group of six patients with subacute meningitis associated with miliary tuberculosis.

Cerebrospinal Fluid Abnormalities. The course of the cerebrospinal fluid abnormalities before, during and after treatment is presented in table 1, where it may be seen that before the intrathecal administration of streptomycin was started, the cerebrospinal fluid findings were those usually encountered in tuberculous meningitis. In addition to the presence of *M. tuberculosis,* the concentrations of sugar were abnormally low (10 to 46 mg. per cent) and the values for total protein and the numbers of cells were appreciably elevated. In general, there was no conspicuous alteration in the amount of chlorides. It is worthy of note that in one patient, tubercle bacilli were cultured from the cerebrospinal fluid when the only other abnormality was an increase in protein (73 mg. per cent). After one month of intramuscularly administered streptomycin, she had developed no clinical manifestations of meningitis, but the values for sugar, cells and total protein had become distinctly abnormal.

TABLE I

Cerebrospinal Fluid Findings before, during and after Treatment in Nine Patients with Tuberculous Meningitis

Name	Pressure			Cells			Sugar			Protein			Cultures		
	Before	During	After	Before	During	After	Before	During	After	Before	During	After	Before	During	After
C. Co.	130	90–130	190	175	9–150	3	46	47–93	60	39	30–72	51	neg.	neg.	+
R. He.	Inc.	Inc.	N.	45	40–1100	312	28	26–62	55	—	115–1125	250	+	neg.	neg.
S. Le.	150	85–150	—	222	30–340	5	43	43–93	103	30	26–116	30	+	+	+
P. Bu.	N.	N.	Inc.	900	90–1300	14	32	16–47	34	73	70–1010	79	+	+-neg.	neg.
	N.	—	—	415	50–900	—	25	16–76	—	105	76–167	—	+	+-neg.	neg.
G. Te.*	100	150	—	60	260	—	29	19	—	82	92	—	+	+	+
A. Ke.	175	50–160	—	44	20–350	—	10	35–71	—	131	80–394	—	+	+	+
E. De.	175	40–200	—	109	45–245	—	33	32–74	—	91	80–285	—	+	+	+
C. Sn.	500	140–650	120	146	66–400	10	10	23–50	55	108	75–443	55	+	0	0
H. Ra.	700	150–300	100	325	30–333	15	20	29–52	50	280	180–403	78	+	0	0

* Treated 3 days only.
Inc. = Increased.
N. = Normal.

In the entire group, the principal changes in the cerebrospinal fluid after the start of intrathecal therapy consisted of the disappearance of the positive cultures for tubercle bacilli and a gradual increase in the concentration of sugar.

The values for cerebrospinal fluid sugar gradually increased during the first week of intrathecal therapy in five of the patients in whom the sugar was low before therapy. In one, however, the concentration of sugar was not consistently above 40 mg. per cent until after 120 days of treatment.

The cerebrospinal fluid sugars of the others, all of whom had subacute meningitis in association with miliary tuberculosis, remained within the normal range until death.

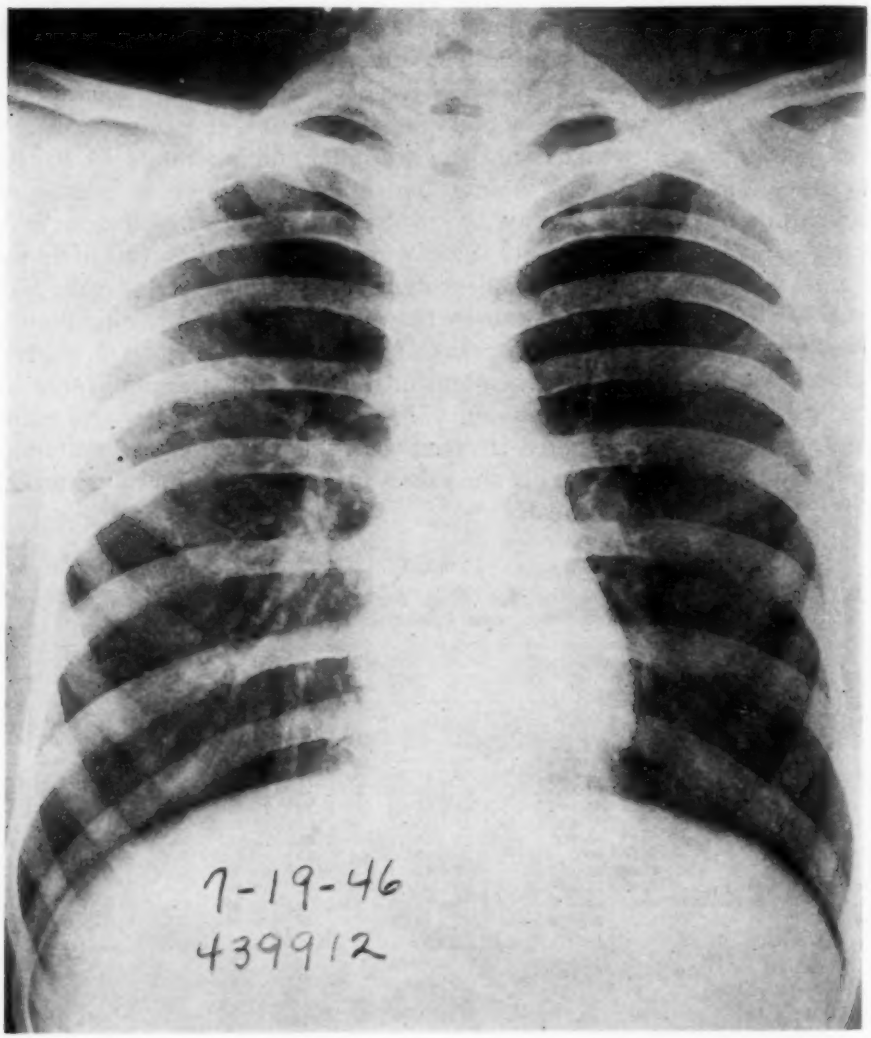

FIG. 4c. Patient C. Co., roentgen-ray of chest just prior to onset of relapse. Note complete clearing of miliary infiltrations and regressions of mediastinal lymph node enlargement.

Except for abnormalities in the quantity of sugar and the presence or absence of organisms, determinations of the various components of the cerebrospinal fluid yielded little information of value during the period of therapy by the intrathecal route. Irrespective of the eventual outcome, the total number of cells and the total quantity of protein remained elevated so long

as the intraspinal treatment was continued. When intrathecal administration was discontinued, the number of cells fell rapidly to within or slightly above the normal range. The diminution in protein, however, was appre-

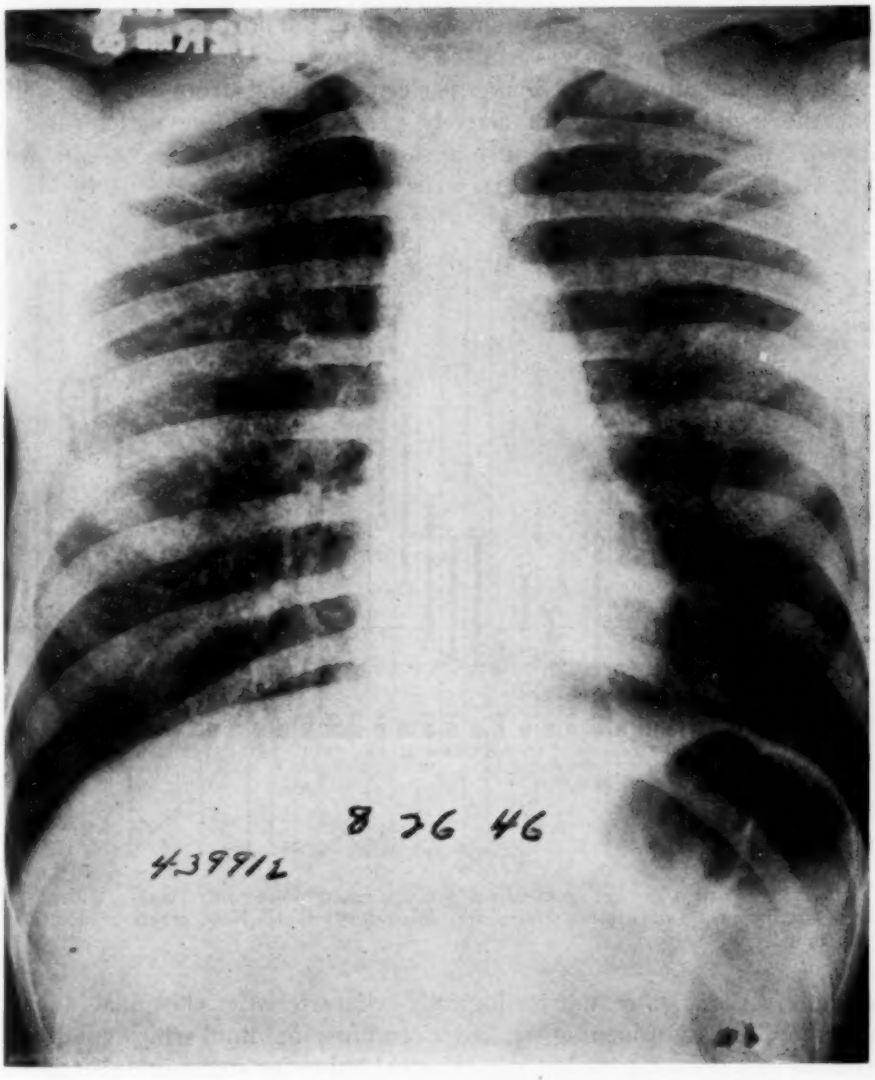

FIG. 4*d*. Patient C. Co., roentgen-ray of chest one week before death showing reappearance of disseminated miliary infiltrations and widening of supracardiac shadow by lymph nodes which at autopsy were broken down and suppurated.

ciably less rapid. In the two patients who experienced sustained remissions, the total protein values were between 68 and 75 mg. per cent, five months after the cessation of all antimicrobial therapy. It is probable that much of

the pleocytosis and some of the elevation in total protein resulted from the irritating effect of repeated intrathecal instillations of streptomycin and not from the meningitis. In accord with this assumption is the fact that in a case omitted from this series because bacteriologic proof of the diagnosis was not obtained, the amount of protein was within the normal range at the time intrathecal streptomycin was started. During the ensuing 60 days, the quantity of protein rose to 177 mg. per cent, although from all other indications the meningitis was not actively progressing. The patient is a 33 year old man who also attained a satisfactory result five months post-treatment. His illness was characterized by high fever (38 to 40° C.), a

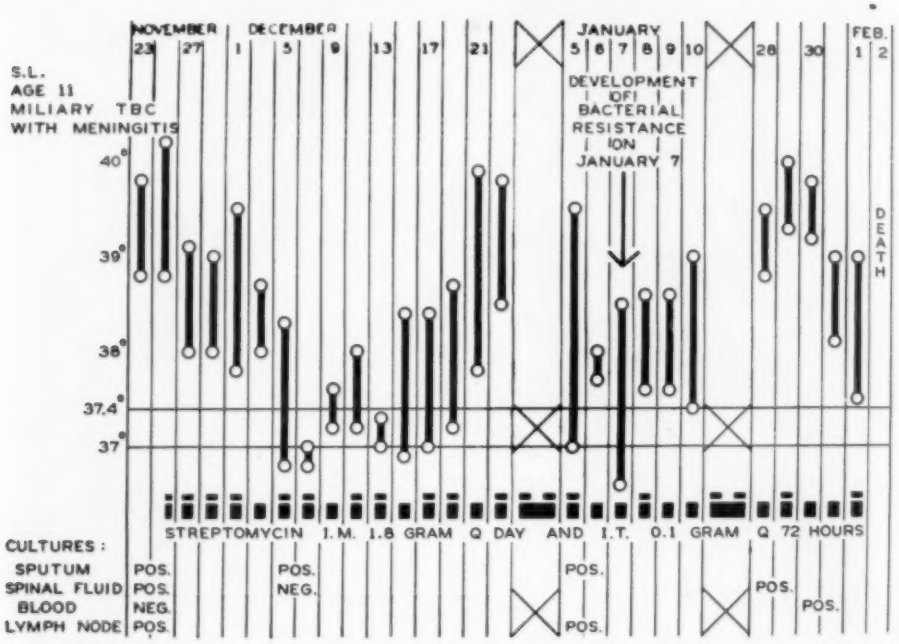

FIG. 5*a*. Patient S. Le., generalized miliary tuberculosis with relapse under streptomycin treatment. Temperature chart and laboratory data. Note positive blood culture preterminally in relapse.

palpable spleen, four morphologically characteristic choroidal tubercles, clinical evidences of meningitis, and a cerebrospinal fluid which contained 70 lymphocytes per cu. mm. but no abnormal value for sugar or tubercle bacilli on smear or culture.

In summary: Two of nine patients with bacteriologically proved tuberculous meningitis attained remissions which have been maintained for five months after the completion of therapy. In all of the seven unsuccessfully treated cases, the meningitis arose as a complication of an acute hematogenous tuberculosis which was the principal cause of death in all but two instances.

Generalized Hematogenous Tuberculosis.

Acute Miliary Tuberculosis. Thirteen patients presented the characteristic clinical and roentgenologic findings of acute miliary tuberculosis at the time streptomycin therapy was started. The etiology of the infection was established by culture or guinea pig inoculation in every member of the group.

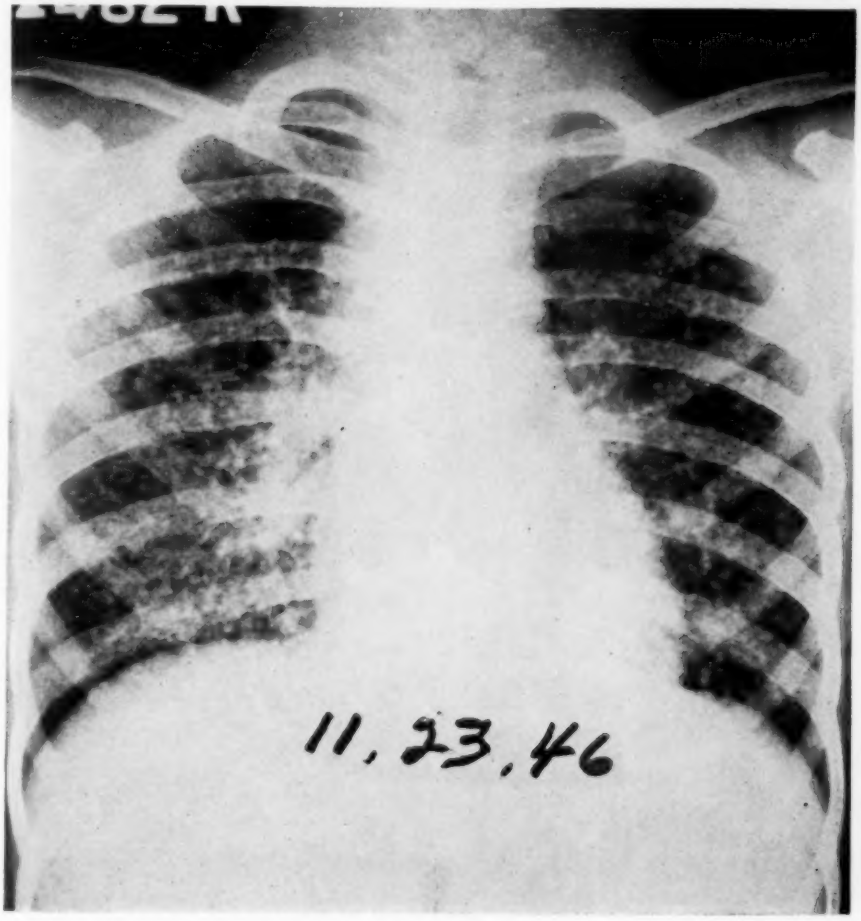

FIG. 5*b*. Patient S. Le., roentgen-ray of chest before start of treatment.

During the first month of antimicrobial therapy, the course of the infection was essentially the same in all of the 13 patients. There was a prompt reduction in temperature, which frequently attained normal levels within a week of the start of treatment. The defervescence was accompanied by a pronounced change in appearance and symptoms. Individuals who had been critically ill before therapy soon presented the aspect of chronicity or re-

covery. In the sicker patients, mental alertness replaced a state which had resembled that observed in severe typhoid. Enlarged cervical lymph nodes, present in five of the group, receded substantially. In only one instance, however, was there an appreciable reduction in the size of enlarged medi-

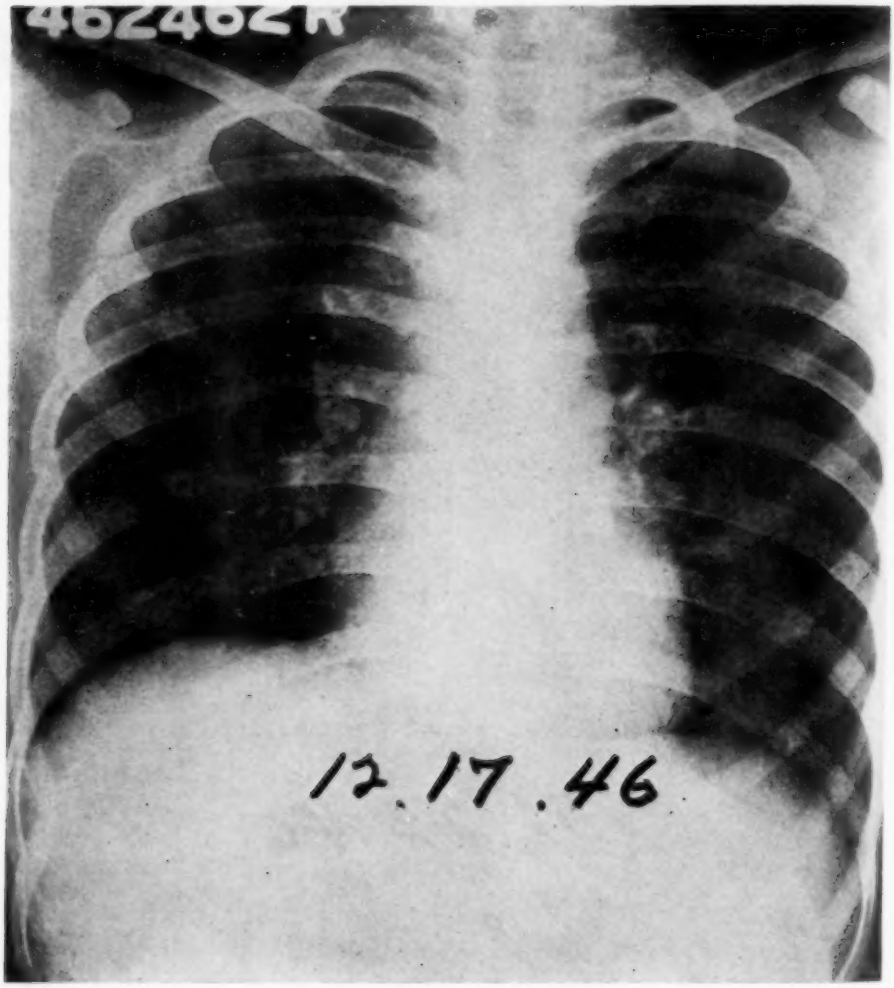

FIG. 5c. Patient S. Le., roentgen-ray four weeks later showing extensive clearing.

astinal nodes. Choroidal tubercles, which had been noted in two patients, regressed considerably during the first month of treatment and eventually disappeared. A weight gain of more than five kilos occurred in three patients, and in the others the weight remained stationary.

The period of rapid clinical improvement was accompanied by a definite reduction in the size of the cardiac silhouette in three patients (figures 6b, 6d

and 6j). Although all of them had been acutely ill at the start of the antimicrobial therapy, they had presented no evidences of pericarditis, or of circulatory failure. This phenomenon remains unexplained.

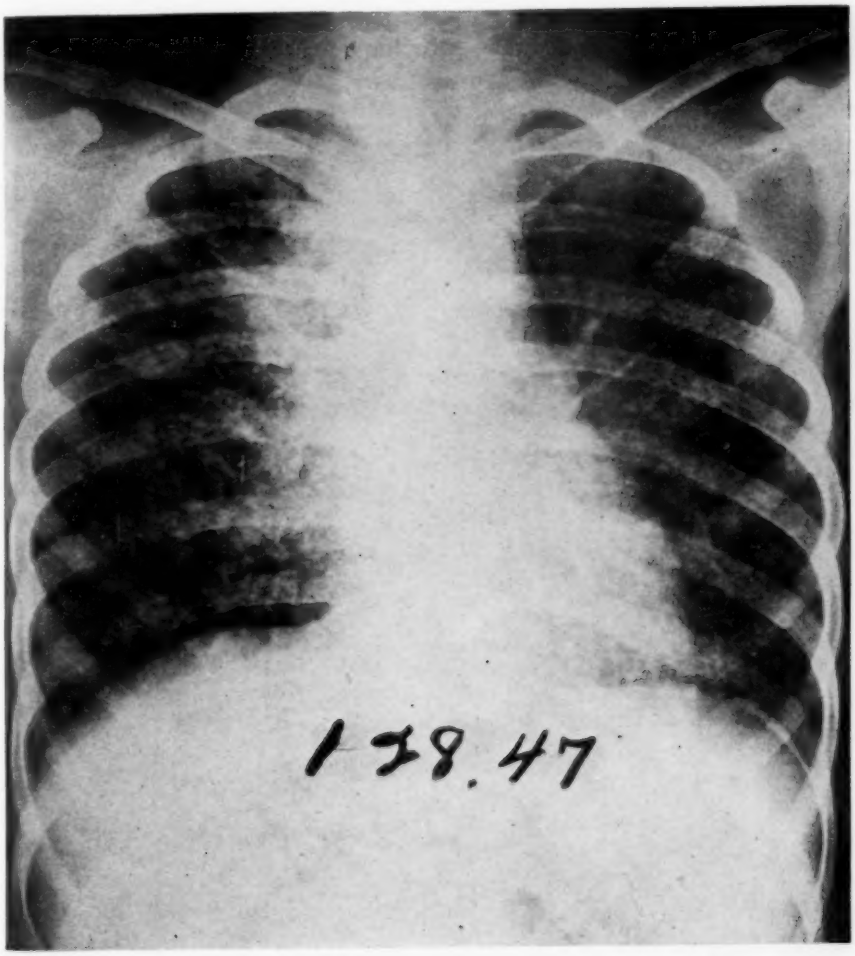

FIG. 5*d*. Patient S. Le., roentgen-ray five days before death showing relapse.

After the initial improvement, which usually continued throughout the first month of therapy, the course of the individual miliary infections followed one of the four following patterns:

1. Continued improvement with attainment of complete remission * sustained for at least six months without therapy;

* Throughout the entire report, the term "complete remission" is used to designate the status of patients who were: asymptomatic; afebrile; discharged no tubercle bacilli; and had absent, stationary, or regressive lesions as determined by roentgenography.

2. Continued improvement with transformation of the acute generalized infection into a chronic disease with residual activity in scattered foci;

3. Continued improvement with sustained remission of the miliary infection followed by fatal meningitis;

4. Partial or complete remission of the signs of infection followed by fatal relapse despite uninterrupted streptomycin therapy.

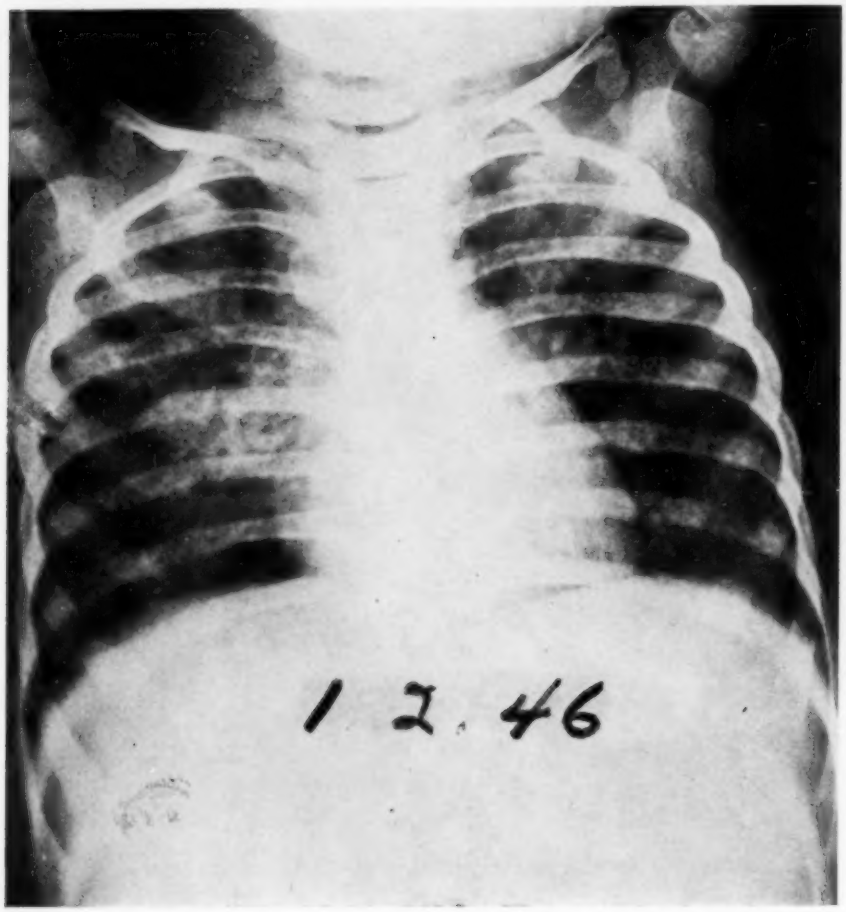

FIG. 6a1.

Complete Remission. Only two of the 13 patients developed complete and sustained remissions of the miliary infections (figures 1 and 2). Both are white adults, and in both the tuberculosis can be classified as apparently arrested, according to the N.T.A. standards,[15] six months after the completion of therapy. In one (A. Fo.), the miliary tuberculosis developed in association with involvement of the cervical and mediastinal lymph nodes.

In the other (R. Ph.), the hematogenous dissemination occurred as a complication of pulmonary tuberculosis which had spread after the first stage of a thoracoplasty three and one-half months before the start of antimicrobial therapy. At the time streptomycin was discontinued, neither showed more than slight roentgenologic evidences of miliary tuberculosis, but the mediastinal lymphadenopathy was still present in one, and the residuum of the

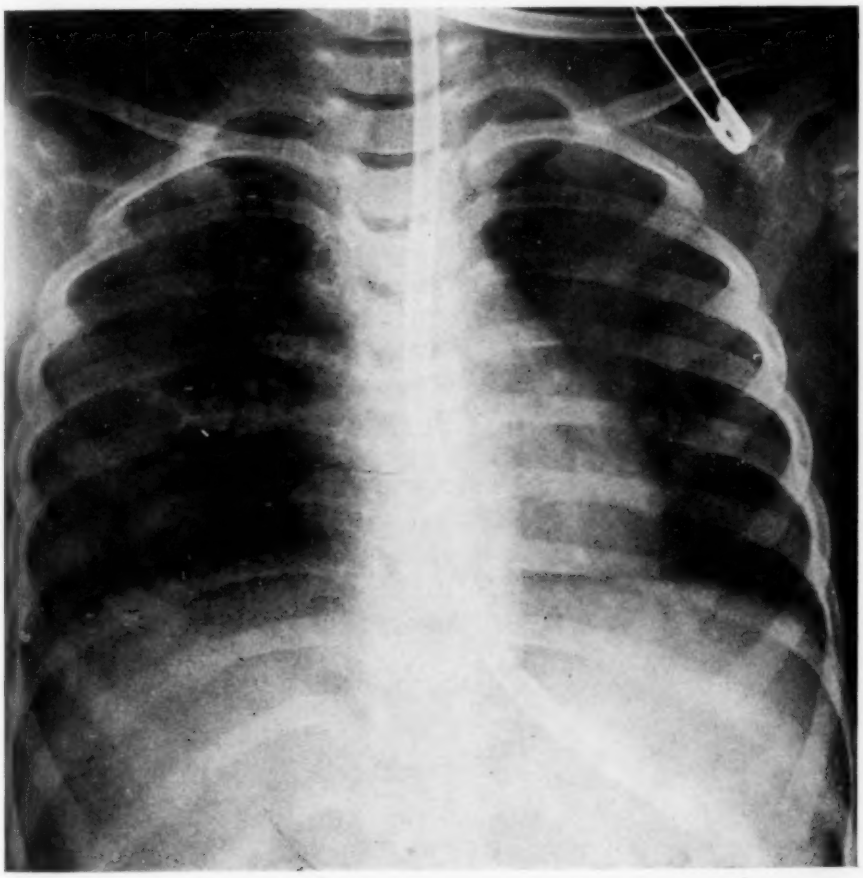

FIG. 6a2.

pulmonary tuberculosis persisted in the other. It is of interest that in each of them there was a virtually complete clearing of these residual processes in the six months subsequent to the completion of the antimicrobial therapy.

Transformation into Chronic Infection with Residual Activity in Scattered Foci. The apparent transformation of the acute miliary tuberculosis into a chronic infection was observed in only one patient, an extremely cachectic and desperately ill woman of 22. After an initial period of improvement manifested by abrupt defervescence and disappearance of choroidal

tubercles, she developed an intermittent fever (37° to 38.5° C.) with the appearance of chronic illness. Repeated cerebrospinal fluid examinations failed to reveal meningitis, but at no time during the first three months of therapy was there clear and definite evidence that she would recover. She improved steadily and gradually during the last month of treatment and in the immediate post-treatment period her improvement was impressive. Her

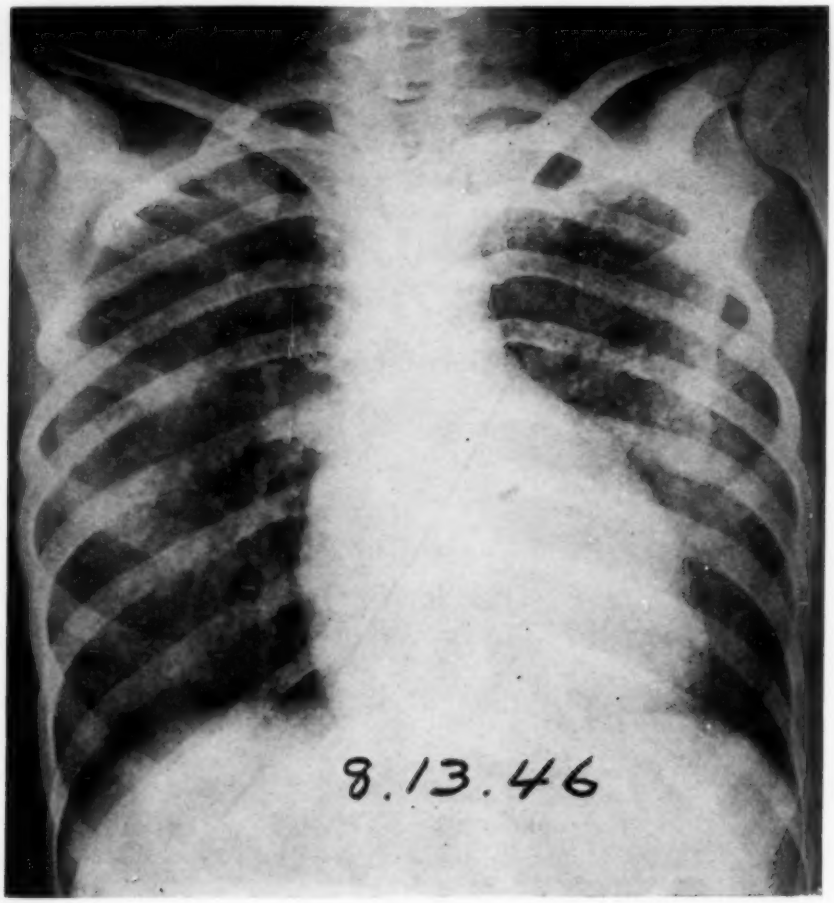

FIG. 6b1.

temperature was maintained in the normal range, and she gained 8.5 kilograms in weight. Ten weeks after the cessation of therapy, she developed signs of pleuritic and pericardial involvement accompanied by a return of fever. Although the possibility of a second hematogenous dissemination cannot be excluded, clinical or roentgenologic evidence was lacking. Streptomycin therapy was reinstituted for a six-week period and was accompanied by prompt defervescence and disappearance of symptoms. During

the two and one-half months since completion of the second course of treatment (10 months after therapy was first started), the patient has remained asymptomatic.

In consideration of the unusual course of this infection, it may be relevant that, in the 10 month period since the start of antimicrobial therapy, no

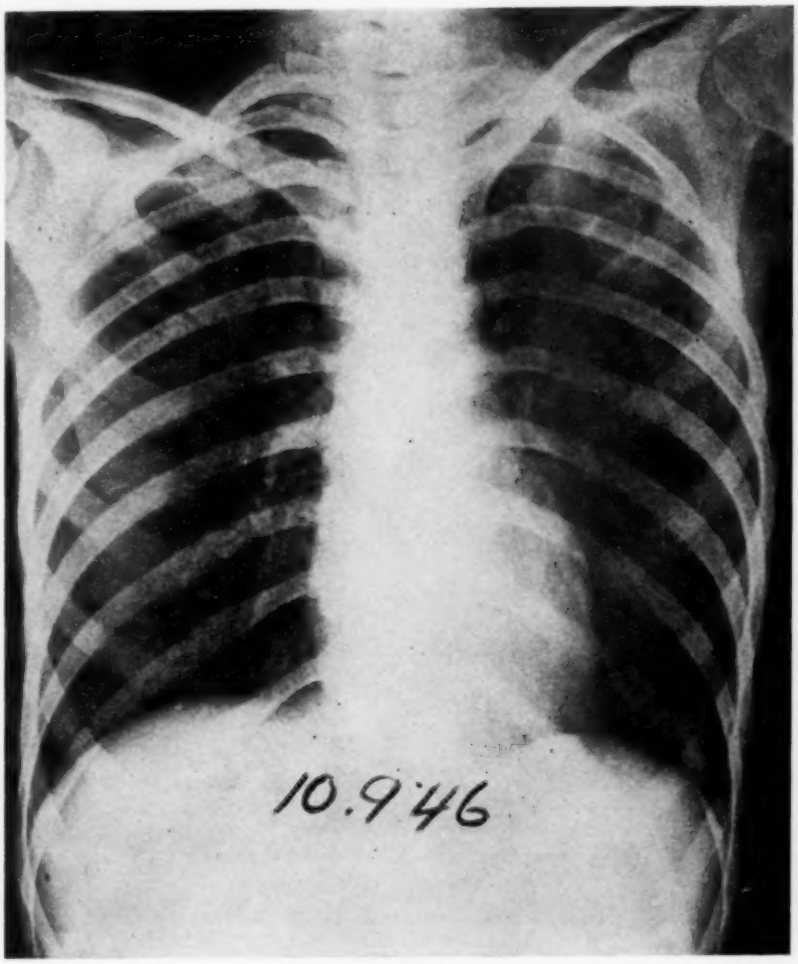

FIG. 6b2.

change in the scattered densities in the roentgenogram has been noted (figure 3). Moreover, each of these densities are two to three times larger than the shadows usually cast by the lesions of miliary tuberculosis. It is established, however, that these large (2 to 5 mm.) densities represented an early process, for they appeared under observation during the four weeks immediately preceding the initial course of streptomycin therapy. This patient's miliary

infection is the only one in the entire series in which marked roentgenologic clearing failed to occur.

Complete Remission of Miliary Infection with Death from Meningitis. Complete recovery from the miliary infection with eventual death from meningitis occurred in only one patient, the 18-month infant whose case has been previously described. The completeness of the recovery from the hema-

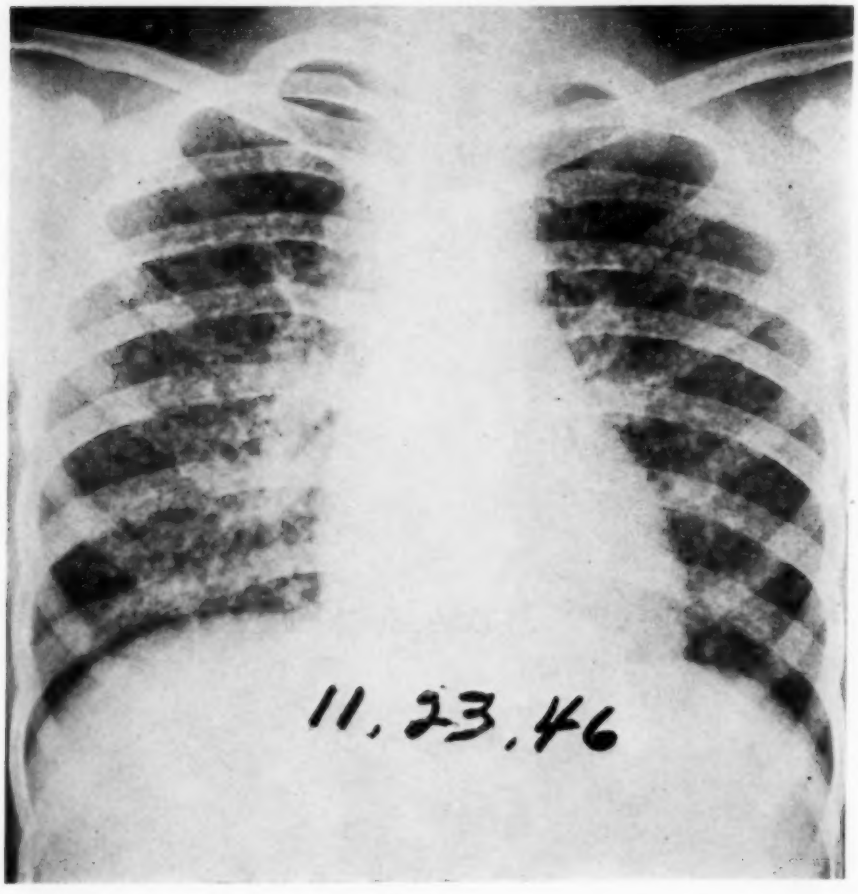

FIG. 6*c1*.

togenous disease was substantiated by the histopathologic findings obtained 11 months after the start of streptomycin therapy. These observations are presented in detail below.

Diphasic Course. The course of infection which was most frequently observed in the entire series was a diphasic type of miliary tuberculosis which eventually resulted in death. The diphasic response occurred in five patients. In all but one instance, the fatal relapse developed while the patient was

receiving streptomycin. The exception was a patient whose fatal relapse appeared 17 days after the cessation of a second course of therapy, and was completely unaffected by the reinstitution of streptomycin.

The first phase of the diphasic course consisted of the period of rapid improvement. During the first month of antimicrobial therapy, there was

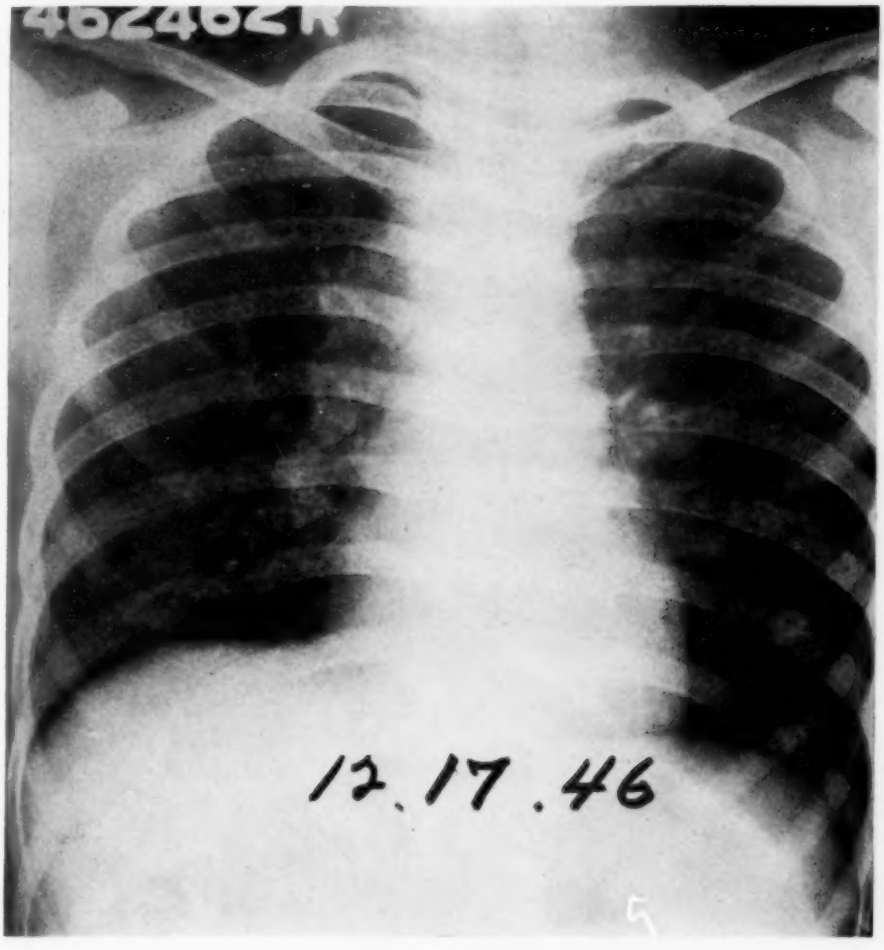

FIG. 6c2.

complete or virtually complete regression of all of the presenting clinical evidences of tuberculous infection. The principal clinical manifestations so affected were: enlargement of the superficial lymph nodes (five patients); pharyngeal and laryngeal lesions (two patients); choroidal tubercles (two patients). The cerebrospinal fluid findings of tuberculous meningitis were present at the start of therapy in two individuals and appeared between the

thirty-fifth and ninety-sixth days of treatment in three others. In these patients, however, the meningitis was never a significant factor in the total illness and, in some instances, produced no clinical manifestations. In all five patients, the clinical improvement was accompanied or followed by an extensive clearing of the miliary densities demonstrable on the roentgenogram.

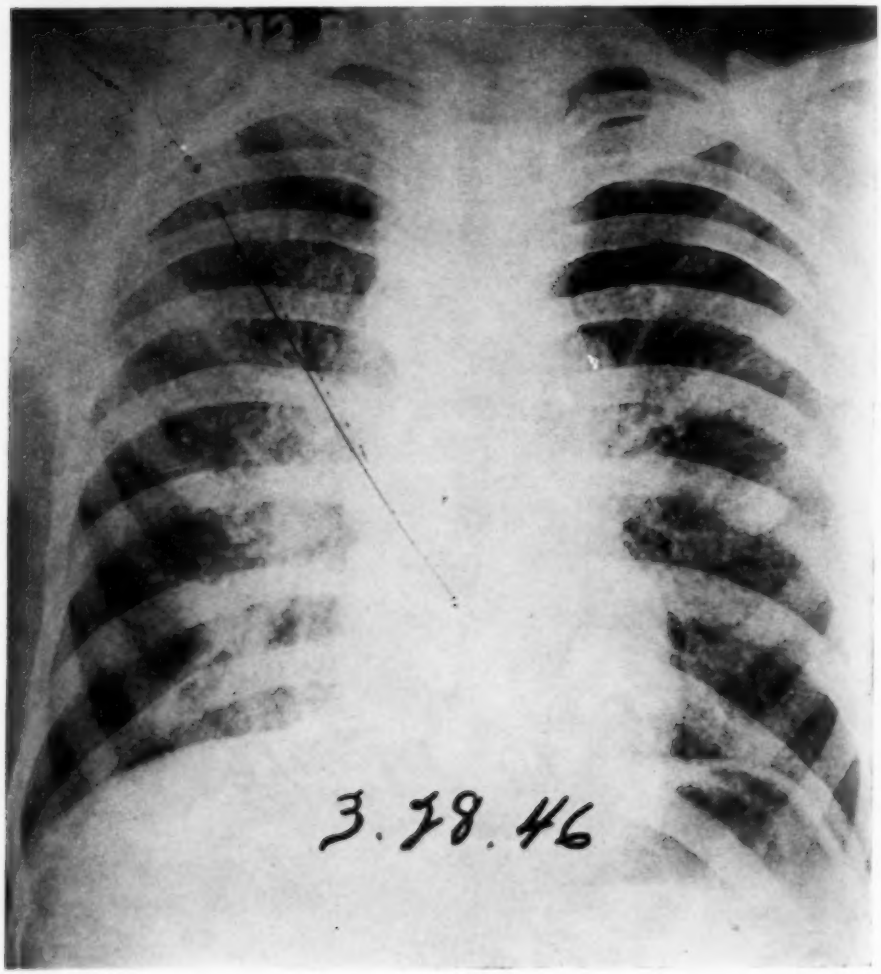

FIG. 6d1.

The extent of both the clinical and the roentgenologic changes varied among the individual patients, but in every member of the group the improvement was marked. Although the majority of the patients did not appear to be completely well, they usually presented no more evidence of disease than a continued low-grade fever. In one patient a complete re-

mission was attained and continued for three and one-half months after the cessation of therapy.

The most extreme example of the diphasic phenomenon, however, was observed in a 21 year old white man (figure 4). After two months of

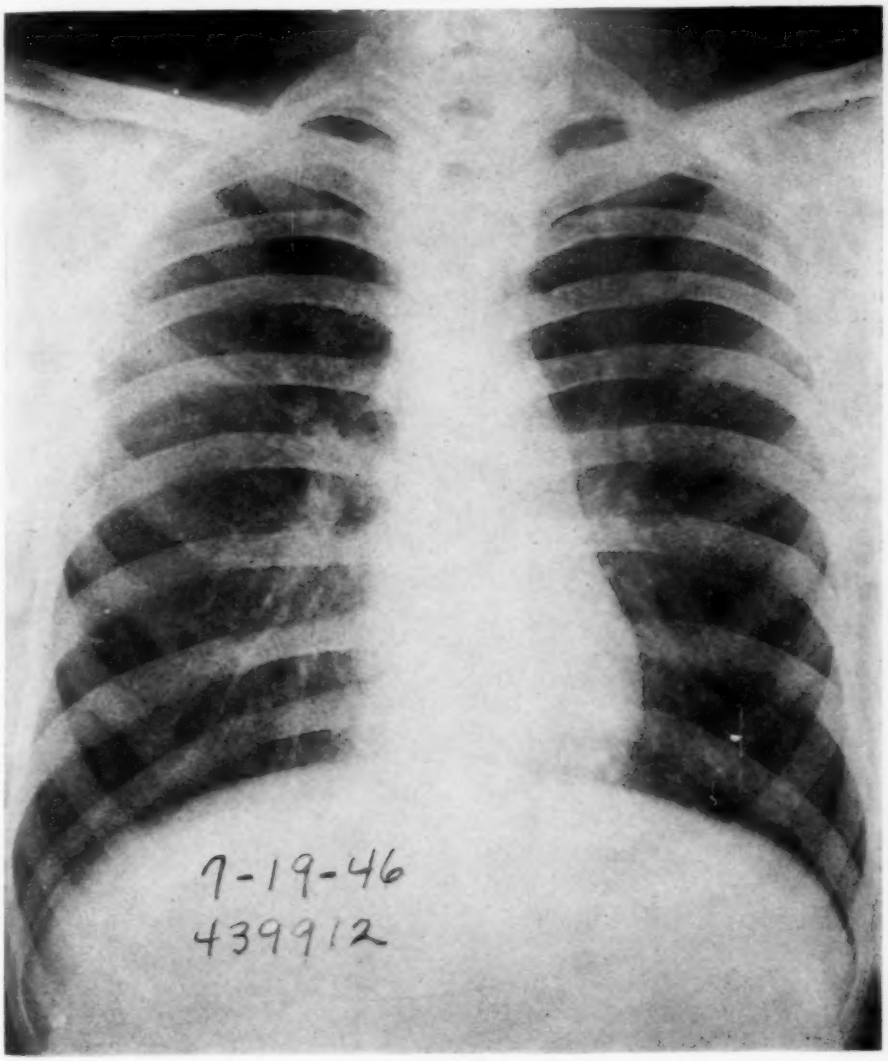

FIG. 6d2.

streptomycin therapy, this patient presented no clinical, roentgenologic or bacteriologic signs of miliary tuberculosis, although all three types of evidence had been present prior to treatment. The complete remission was maintained for approximately five weeks until the beginning of the fourth month

of the use of streptomycin. At this time, although therapy was not interrupted, the cervical lymph nodes enlarged and discharged bacilli, fever returned, and the miliary densities were again visible upon the roentgenogram. The infection resumed the rapidly progressive character which it had displayed before treatment, and the patient died at the end of the fifth month of

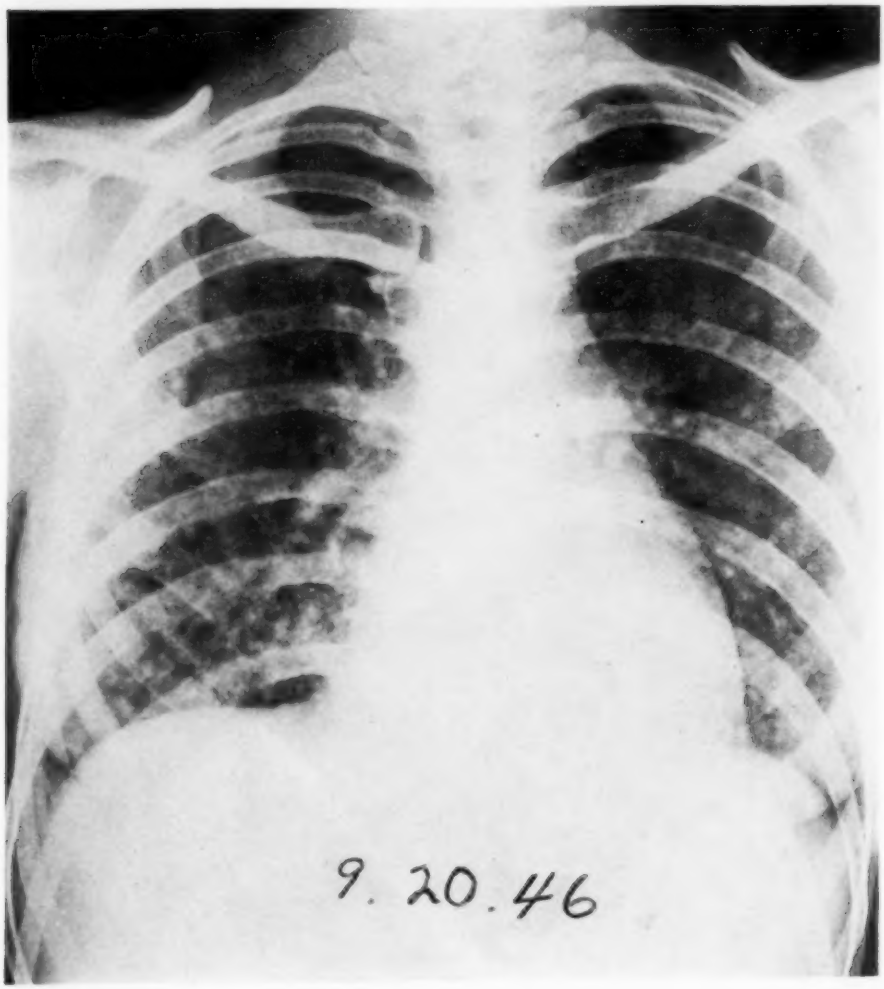

FIG. 6e1.

streptomycin therapy. During the last 10 days of life he was given nine grams of streptomycin daily with no apparent effect upon any manifestation of the infection.

In the other three patients in whom relapse appeared while under therapy, the onset of the phenomenon appeared on the twentieth, fifty-second and

sixty-sixth days of therapy respectively. The onset was heralded by a return or an increase in fever, and by the reappearance of clinical signs of tuberculosis such as enlarged lymph nodes or ulcerative pharyngeal lesions which, in some instances, had been present before the initial generalized hematogenous infection. Approximately two to three weeks after the first

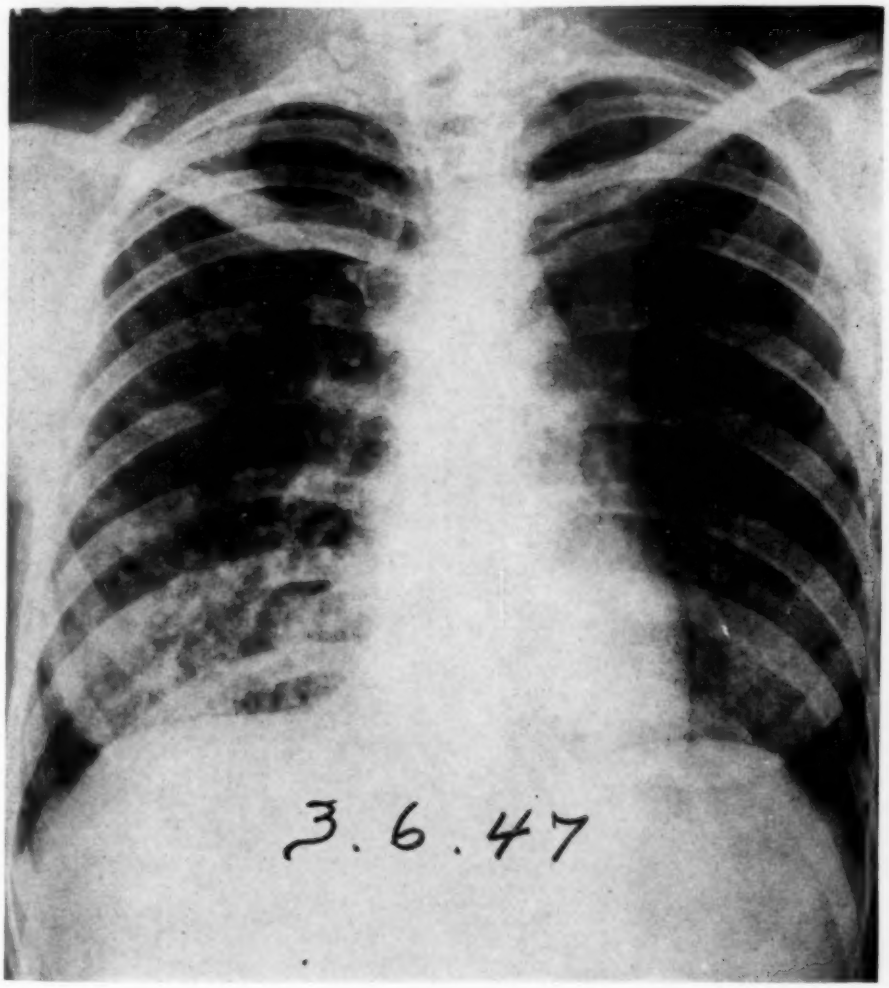

FIG. 6e2.

sign of relapse, the miliary densities reappeared on the roentgenogram. All signs of infection steadily progressed despite the antimicrobial therapy, and, in all four individuals, death occurred between the thirty-eighth and fiftieth days after the onset of relapse.

The demonstration of a bacteremia in one patient (figure 5) and the

appearance of choroidal tubercles for the first time in another is evidence that in some instances a fresh hematogenous dissemination occurred in association with the relapse.

Two episodes of relapsing miliary tuberculosis occurred in the fifth member of the group. The first relapse developed three and one-half months

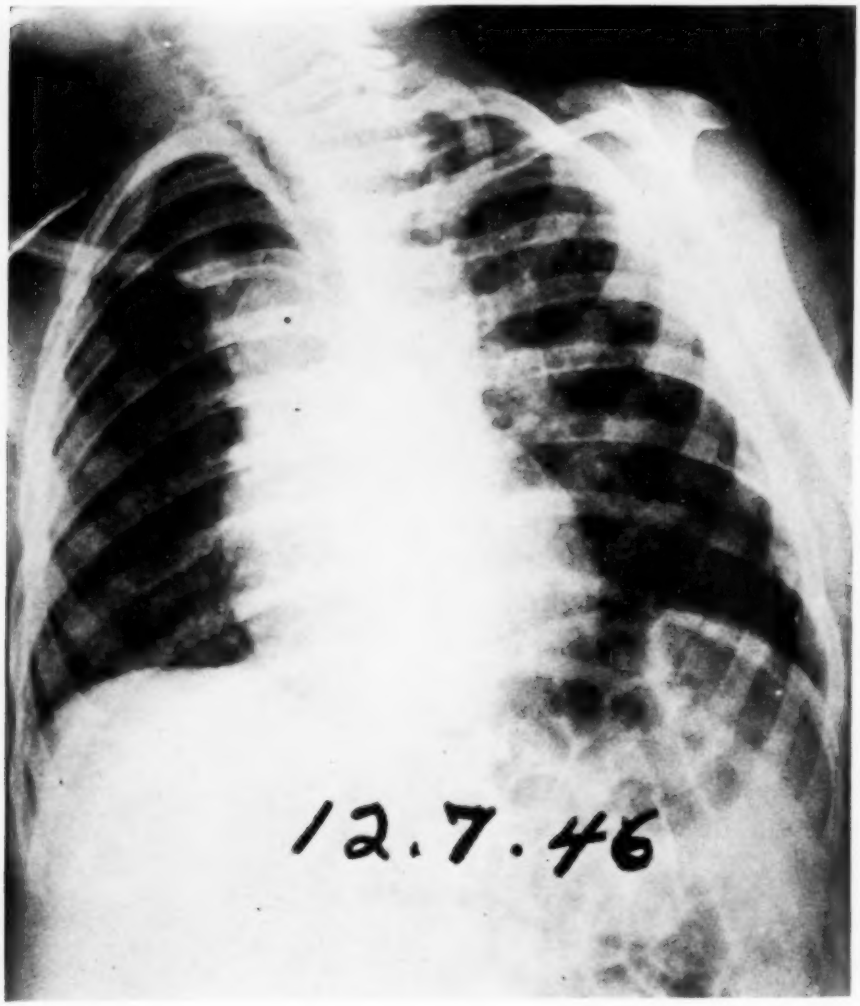

FIG. 6f1.

after a 60 day course of therapy, and appeared to respond to the readministration of streptomycin. The second appeared 17 days after the cessation of a 90 day course of treatment, and was completely uninfluenced by the further administration of antimicrobial therapy. Death occurred within five days of the start of the third course of streptomycin (i.e., 119 days after the start of the 90 day course of therapy). It is probable that this relapsing in-

fection proceeded by the same mechanism as was operative in the other four cases.

Tubercle bacilli isolated from four of the five patients at the onset of relapse under therapy were highly resistant to streptomycin in vitro. Organisms could not be cultured from the other individual at the exact onset of

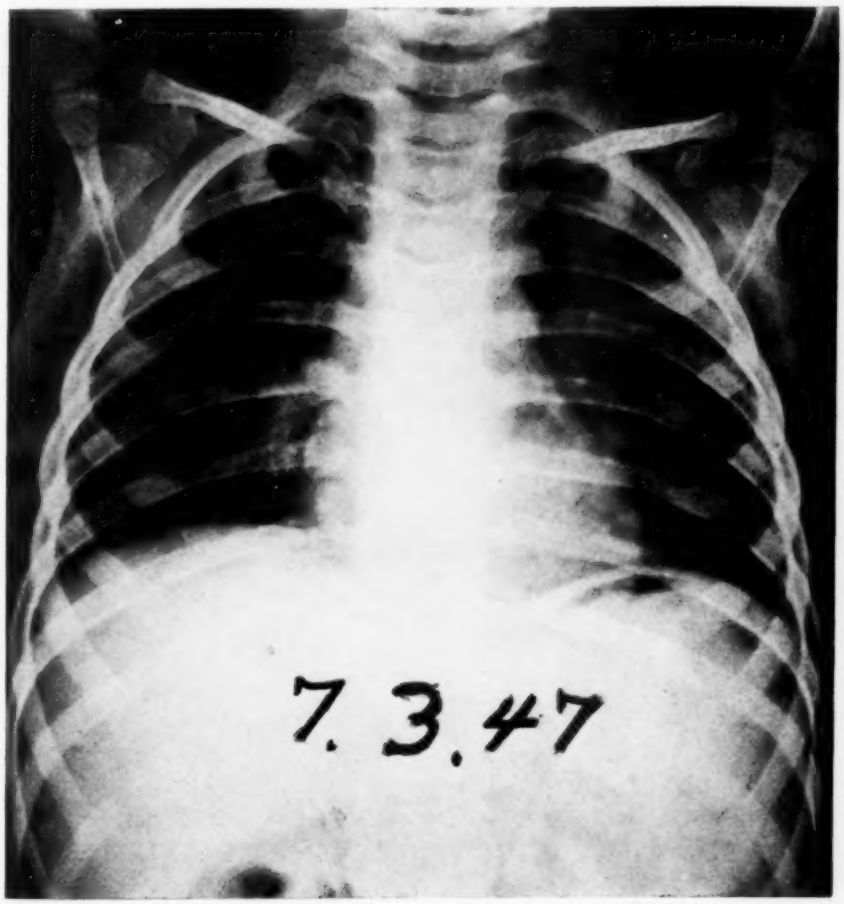

FIG. *6f2*

relapse. Postmortem cultures of the lungs of this patient yielded tubercle bacilli which grow so poorly on artificial media that satisfactory streptomycin sensitivity determinations have not been possible.

Roentgenologic Changes in Acute Miliary Tuberculosis. The roentgenologic changes which were observed in 11 patients with acute miliary tuberculosis are presented in figure 6.* In a few instances, a considerable

* Figure 6 consists of 11 pairs of films (*6a1–6a2, 6b1–6b2,* etc.). The first film in each pair shows the extent of the miliary process prior to therapy and the second the extent of clearing. The second film is not necessarily the earliest film taken that showed extensive clearing. Refer to pages 788 to 813.

amount of clearing occurred during the first month of therapy. In general, however, there was little or no change until the second month of treatment, which represented the period during which the maximum degree of change occurred in the group as a whole. Regardless of outcome, a complete disappearance of the densities of the miliary tuberculosis occurred in eight in-

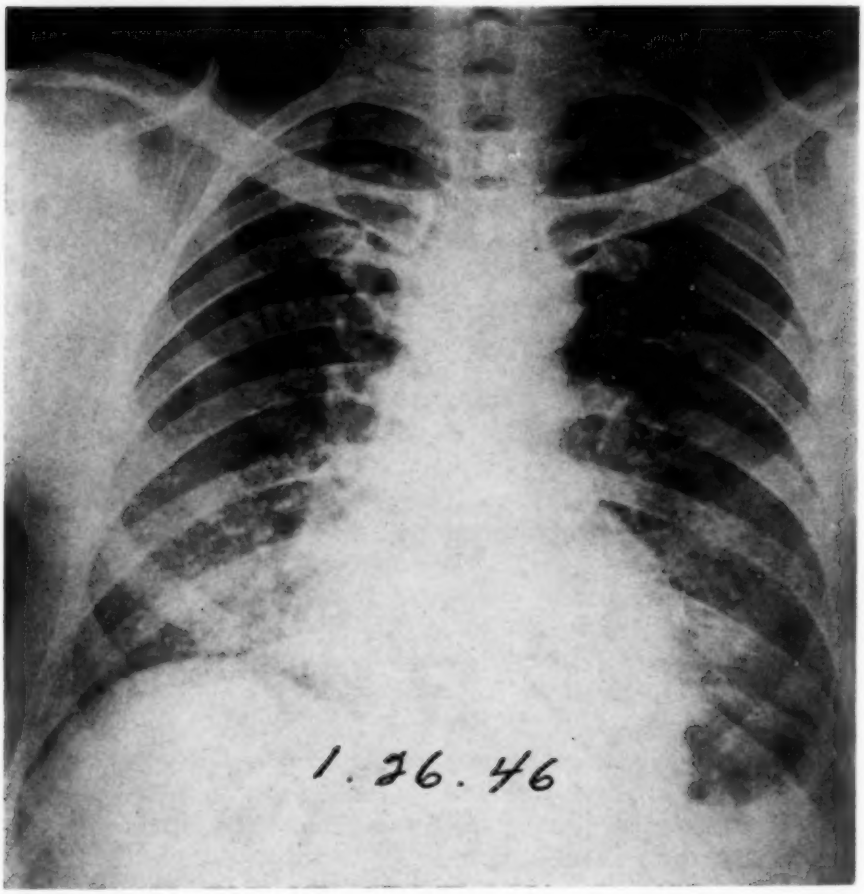

FIG. 6g1.

dividuals at some time during treatment. In the course of relapse, densities were observed to reappear in two to four weeks after the most recent previous film. As noted previously, in one patient there was no demonstrable change in the densities throughout a 10 month period of observation.

Other Hematogenous Forms (Non-Miliary). Two patients presented the clinical picture of an acute hematogenous infection, but never developed the characteristic roentgenologic findings of acute miliary tuberculosis. One had tuberculous pericardial effusion associated with lymphadenitis and bac-

teremia; and the other had disseminated lesions of bone associated with long-continued high fever.

In both, the institution of streptomycin therapy was followed by a reduction in fever and a marked improvement in general appearance and symptoms. In the patient with the widespread lesions of bone, all but one of 11 ex-

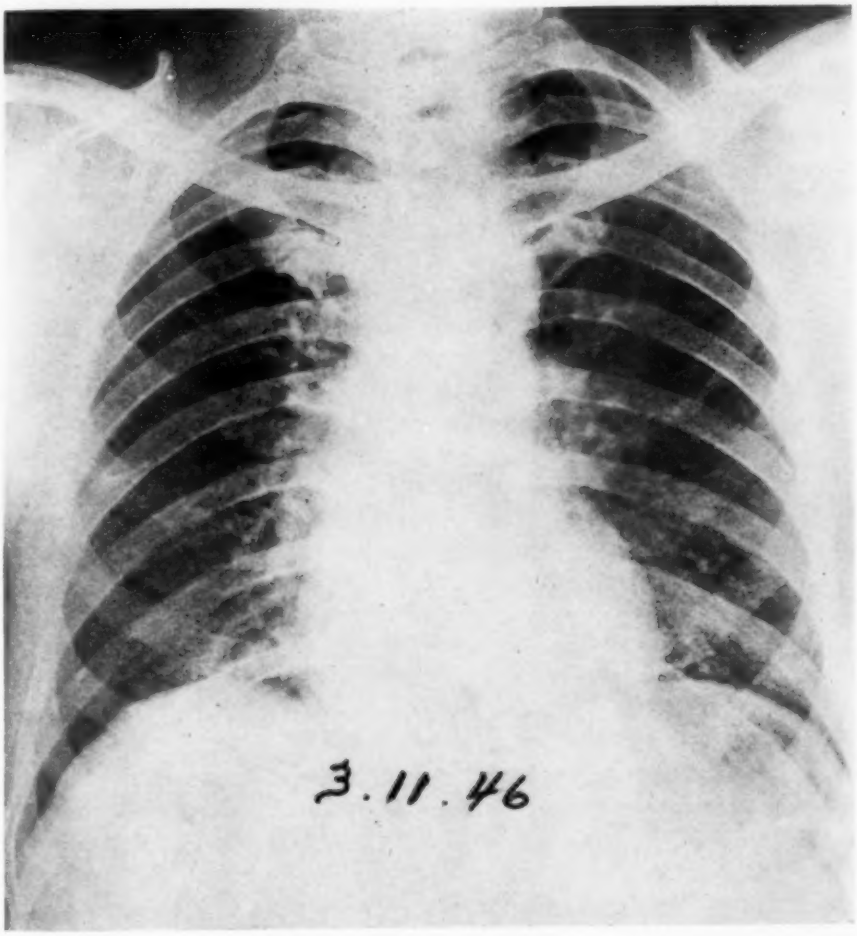

FIG. 6*g2*. Same patient as figure 6*g1*, showing extensive clearing.

ternally draining sinuses healed completely within the first eight weeks of antimicrobial therapy and the remaining one healed thereafter. The cutaneous fistulae have remained closed during the eleventh-month period since the start of streptomycin therapy. There has been no change, however, in the roentgenologic appearance of the various scattered lesions of the bones. It is of interest that at no time did this patient show any roentgenologic or bacteriologic evidence of tuberculosis of the lungs.

The patient (figure 7) with tuberculous pericarditis is a 19 year old colored girl who developed an acute tuberculous pericarditis with effusion during the third month of a rapidly progressing tuberculosis of lymph nodes. Tubercle bacilli were cultured from pericardial fluid, lymph node, and on one occasion from the circulating blood, prior to the institution of streptomycin

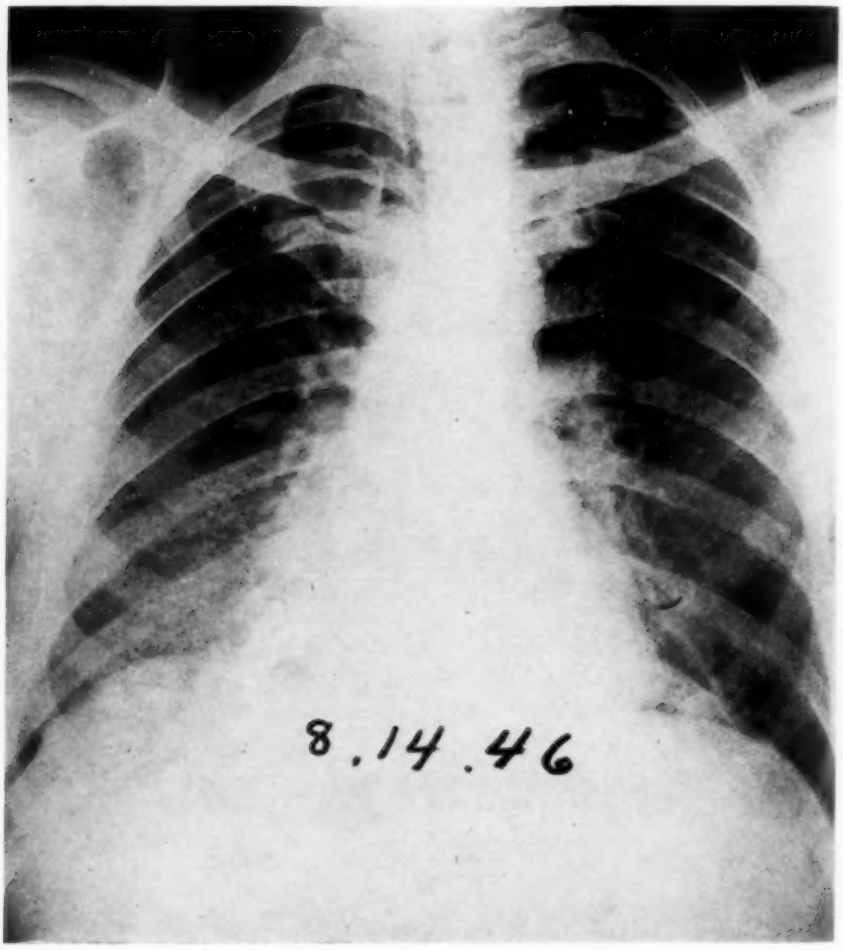

FIG. 6g3. Equally striking change when patient was retreated after relapse.

therapy. Immediately before treatment, the patient was acutely ill and unable to lie flat in bed, although frank signs of cardiac compression were not present. Pericardesis was performed in the week preceding the start of antimicrobial therapy and 100 c.c. of fluid were removed on that occasion. Subsequent aspirations, after the start of treatment, were performed not because of tamponade but in order to obtain specimens for streptomycin assay.

During the first five days after the start of antimicrobial therapy, there was a prompt fall in temperature which was associated with a complete disappearance of symptoms. The clinical improvement was maintained and it became impossible to isolate tubercle bacilli by culture. There was a gradual reduction in the size of the cardiac shadow during the four months

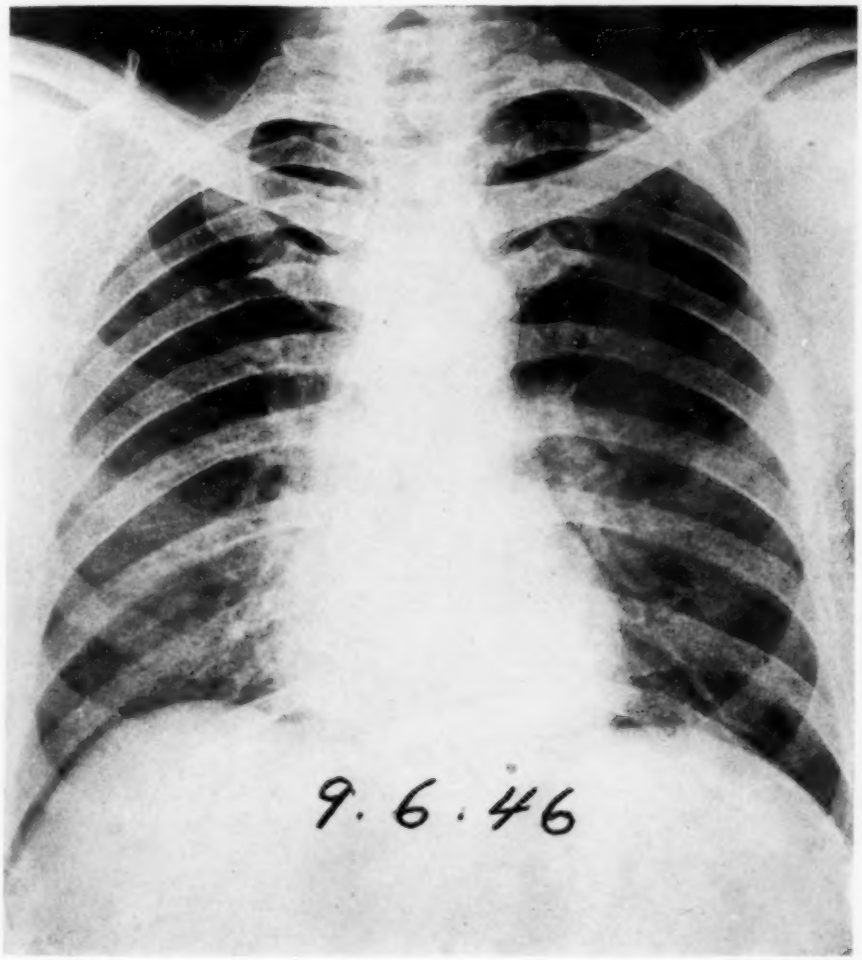

FIG. 6g4. Same patient as preceding figure.

period of therapy. In the ensuing months, still further reduction occurred but an enlargement of approximately 15 per cent persisted. The shrinkage of the cardiac shadow was not followed by any signs of constrictive pericarditis.

Eleven months after the completion of therapy the patient is afebrile,

asymptomatic, has negative cultures, and is leading an ambulatory existence at home.

Streptomycin Sensitivity. Of the entire group of 17 patients with bacteriologically proved generalized hematogenous or meningeal infections, it was possible to determine the streptomycin sensitivity of the pre-treatment

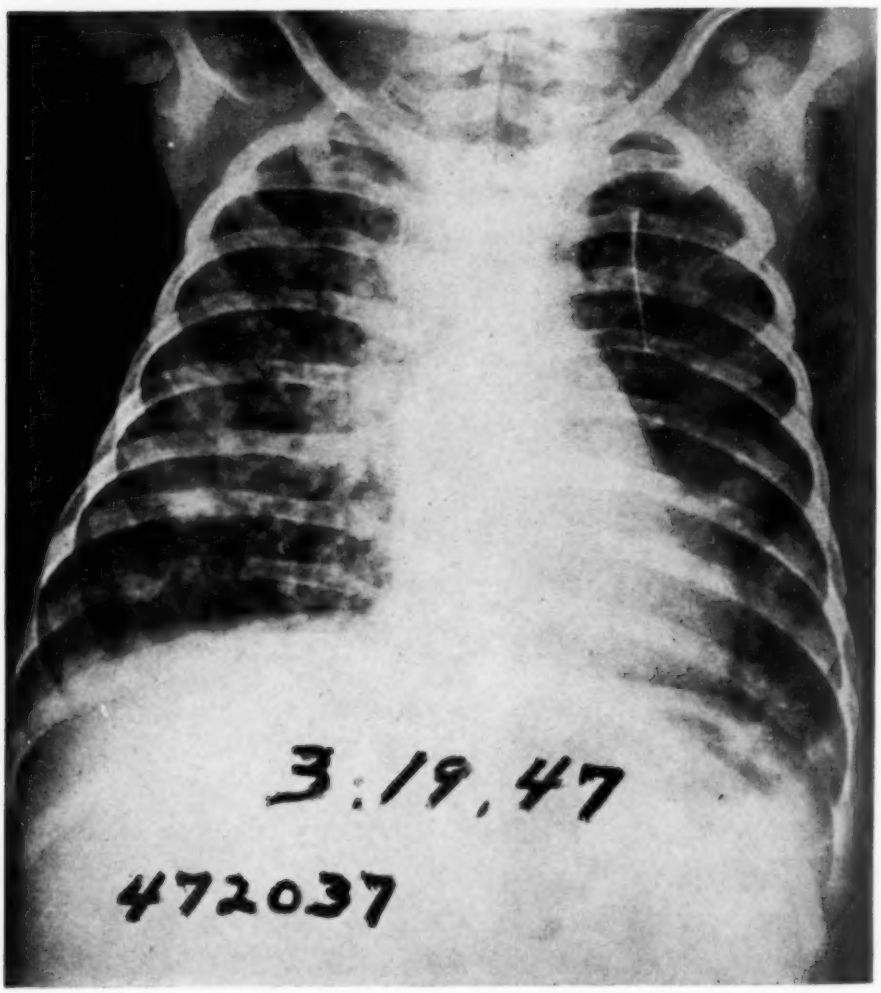

FIG. 6*h1*.

strains of tubercle bacilli in all but two. The results are presented in tables 1 and 3. Organisms cultured from the cerebrospinal fluid are considered separately from the bacilli isolated from sputum, gastric washings, lymph nodes, and the circulating blood. The reason for this distinction lies in the fact that, with the intrathecal administration of streptomycin, the organisms

within the central nervous system have a potential exposure to streptomycin concentrations as high as 1500 to 2500 micrograms per c.c. of cerebrospinal fluid. In contrast, after intramuscular administration of 3.0 grams daily in divided doses, the organisms resident in tissues other than the central nervous system are seldom exposed to streptomycin concentrations greater than 50 micrograms per c.c. of plasma or extracellular fluid.

TABLE II

In Vitro Streptomycin Sensitivity of Cultures from Generalized Hematogenous Infections Exclusive of Meningitis

Patient	Source of Culture	Pre Treatment	Months After Start of Intramuscular Therapy								Remarks
			1	2	3	4	5	6	7	8	
A FO	Lymph node	S									Subsequent cultures of lymph node, gastric washing, blood and urine were all negative
C ST	Blood	S									
	Pericardial fluid	S	OO								No pericardial fluid obtained after second week
J WA	Gastric washing	S			O	O	O				Subsequent cultures of gastric washings negative to date
G MU	Cutaneous sinus	S		O	O	O					No material for culture available after 3 months
A KE	Sputum	S		S*							
R PH	Sputum	S	O	OO	S	O	O O	O OO	O	O	
G TE	Sputum	S		R R	R						Died 4th month
S LE	Abscess	S		R	R*						
	Blood	O				R					
	Urine	S		R							
E DE	Sputum	S			R	R*					
C CO	Lymph node	S					R	R*			
	Gastric washing	S	O	O		I					

O—Negative culture
S—Sensitivity < 2 mcg./c.c.
I—Intermediate sensitivity
R—Resistant > 500 mcg./c.c.
*—Postmortem culture

In table 2 may be seen the streptomycin sensitivities of bacilli obtained from the systemic infection of 10 patients with generalized hematogenous tuberculosis (8 with miliary infections). All of the strains tested before treatment were completely inhibited in vitro by streptomycin concentrations of less than two micrograms per c.c. of medium.

In six cases, organisms could not be isolated after the end of the second month of antimicrobial therapy, and all organisms obtained before that time were streptomycin-sensitive in vitro. (One patient died after only 40 days of treatment and organisms obtained at death were still sensitive to strepto-

mycin.) In the only other fatality (post-meningeal hydrocephalus), tubercle bacilli could not be cultured from the tissues post mortem.

In four patients from whom organisms were obtained subsequent to the sixtieth day of treatment, the bacilli were not inhibited in vitro by concentrations of 500 micrograms of streptomycin per c.c. of medium.* The results of the tests of the organisms obtained at post mortem from the fifth patient were equivocal. All of this group of five died as a direct consequence of the tuberculous infection. The shortest period required for the appearance of a resistant strain was 34 days.

TABLE III

In Vitro Streptomycin Sensitivity of Cultures from Cerebrospinal Fluid

Patient	Pre Treatment	Months After Start of Intramuscular Therapy								Remarks
		1	2	3	4	5	6	7	8	
H RA	S	OOOO	OOO	OO						
C SN	S	SOOO	OOOO	OOOO	OOOO	O		O		
S LE	S	O O	O O							Died 68 days after treatment started
R HE				SO O	OO	O	O			
A KE	S	S OO	OI*							
E DE			S	SSSS	R					Died 101 days after treatment started
G TE			S	S	R					Died 100 days after treatment started
C CO		O	O	OO		O R*				
P BU			S	SO	OOOS	OOOO	O	S	OOS	Second course of therapy started at end of 7th month. Cultures subsequent to 8th month negative

O—Negative culture
S—Sensitivity < 2 mcg./c.c.
I—Intermediate sensitivity.
R—Resistant > 500 mcg./c.c.
*—Postmortem culture

Seven of the 10 patients with hematogenous infections also had tuberculous meningitis. The in vitro streptomycin sensitivities of the organisms obtained from the cerebrospinal fluids of these seven patients and from the two others who did not have hematogenous tuberculosis are presented in table 3.

The results are essentially the same as those observed in the systemic infections. The appearance of in vitro resistance was noted in all three in whom the organisms persisted in the cerebrospinal fluid. At the time the phenomenon appeared, organisms obtained from the systemic infections of these three individuals were similarly resistant to streptomycin in vitro. It is noteworthy, however, that, in two, the strains first isolated from the cere-

* In the subsequent discussion the term "streptomycin-resistant" is used to designate strains of bacilli which are not inhibited by 500 micrograms per c.c.

brospinal fluid were drug-sensitive even though organisms from the corresponding systemic infections were highly resistant to streptomycin in vitro. In these two cases, the organisms from the systemic infection had been demonstrably resistant in vitro (insensitive to 500 mcm. per c.c.) for periods of 18 and 46 days when the streptomycin-sensitive bacilli were first isolated from the cerebrospinal fluid. Moreover, in one of these infections, the

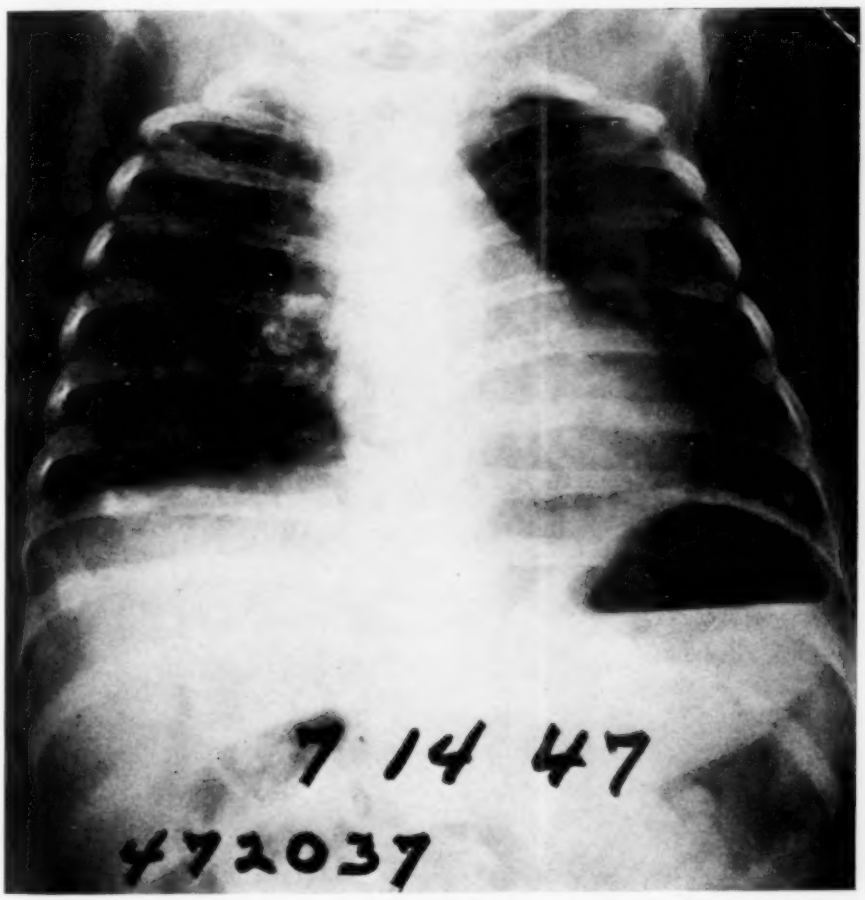

FIG. 6*h2*.

organisms from the cerebrospinal fluid remained streptomycin sensitive for at least 28 days after the start of the intrathecal administration of the drug.

In these observations, the appearance of drug-resistant bacilli within the central nervous system was not noted until the systemic infection had progressed to a terminal stage. As a result, it was not possible to follow the course of the meningitis itself after the development of drug-resistant (meningeal) organisms. It was also impossible to draw inferences con-

cerning the speed of conversion from drug-sensitive to drug-resistant strains of bacilli because the possibility of terminal reinvasion of the central nervous system by organisms from the systemic infection could not be excluded. For example, in one instance drug-resistant bacilli were first obtained from the

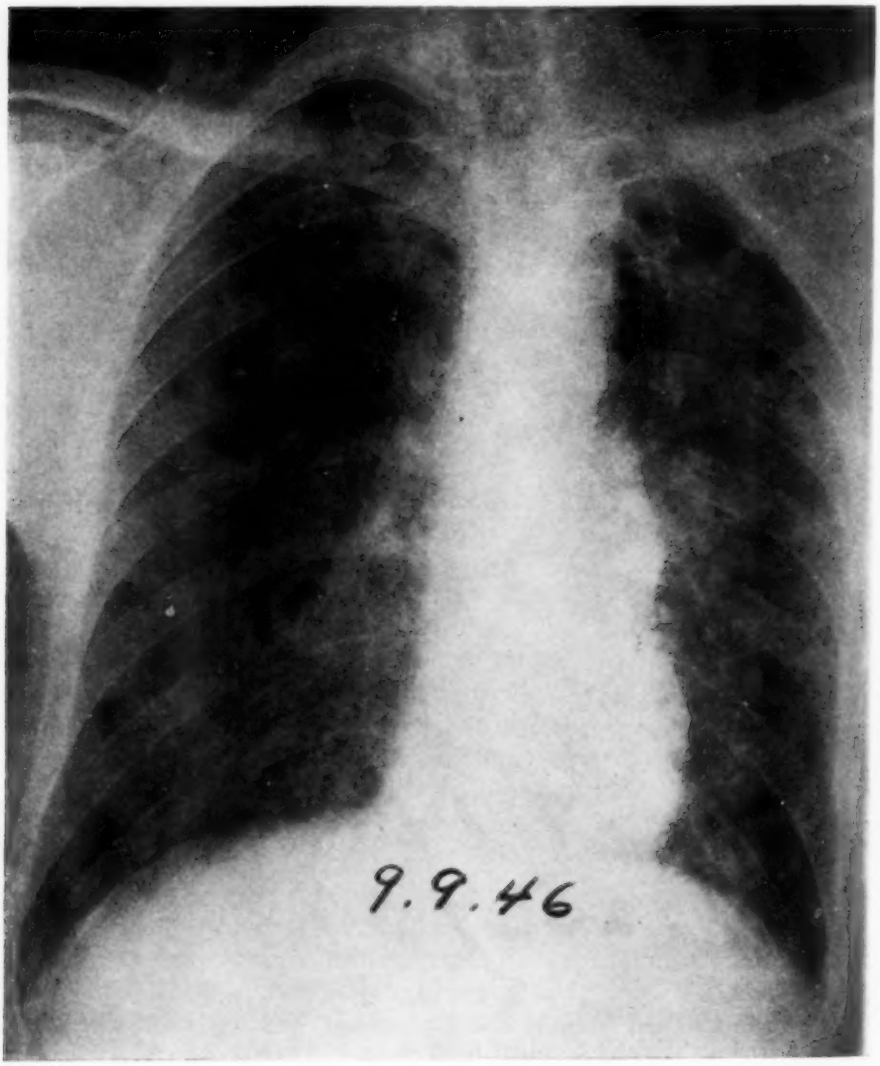

FIG. 6*il*.

cerebrospinal fluid only four days after the isolation of a sensitive strain from the same source. In the 30 days preceding the last isolation of the sensitive strain, 17 similar isolations were also sensitive. As, during the entire period, organisms from the systemic infection were highly resistant, it is

possible that the sudden appearance of drug-resistant bacilli in the central nervous system just before death may have merely represented a recent metastasis.

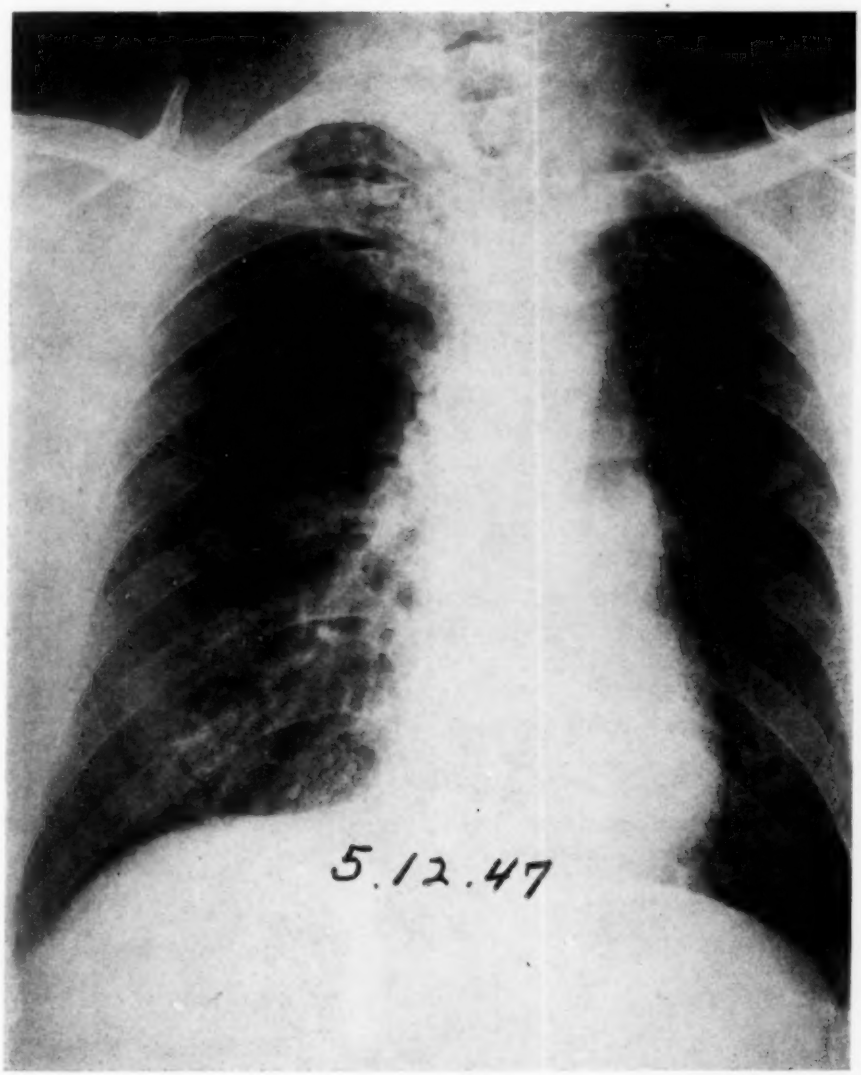

FIG. 6i2.

Correlation between in Vitro and in Vivo Streptomycin Sensitivity. In this series of 15 patients with generalized hematogenous tuberculosis, there was a correlation between failure of therapeutic response and the appearance of drug resistance as demonstrable in vitro.

Tubercle bacilli which were resistant to streptomycin in vitro were

obtained from a total of four patients with miliary infections. Despite streptomycin therapy, all four of them died as a direct consequence of the miliary disease. During the first one or two months of antimicrobial therapy, before in vitro streptomycin resistance was demonstrable, these four patients presented the same unprecedented clinical, roentgenologic and bacteriologic

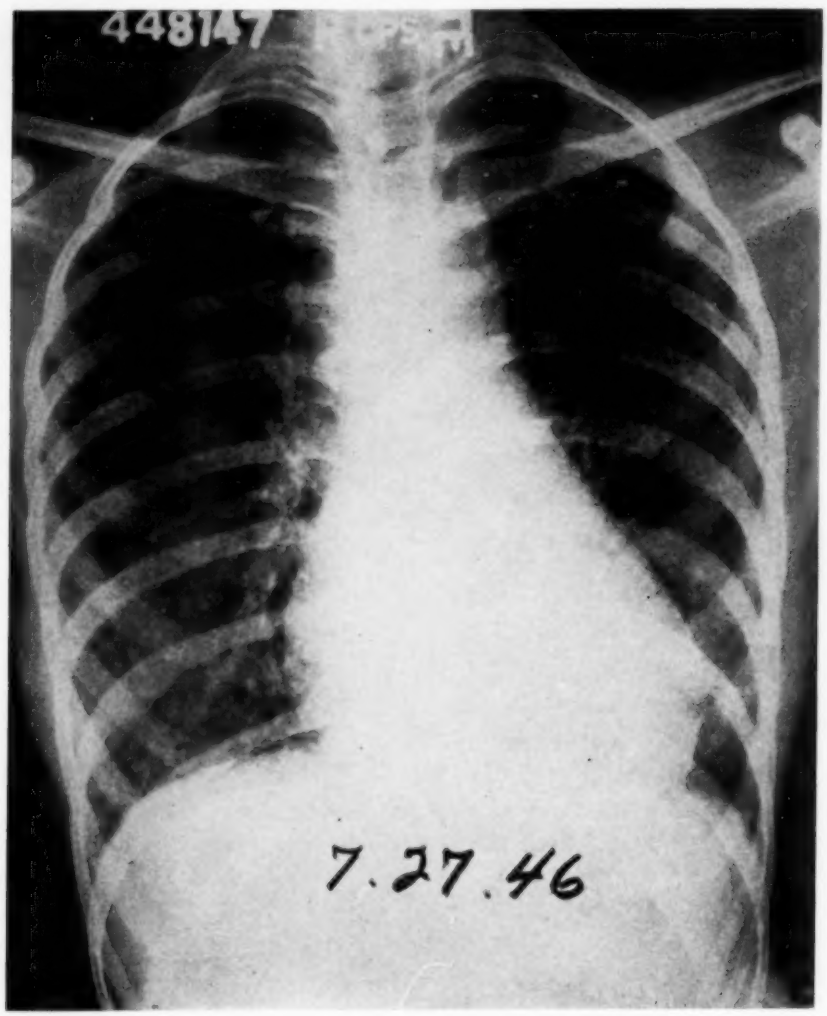

FIG. 6*j1*.

improvement as was observed in the others whose remissions were sustained. In all four of the patients with drug-resistant bacilli, however, relapse occurred during a period of uninterrupted streptomycin therapy. Moreover, as noted previously, the time of appearance of clinical relapse coincided with the first detection of organisms which were streptomycin-resistant in vitro.

In contrast to the apparent therapeutic response during the early phases of treatment, these relapsing infections were completely uninfluenced by the further administration of streptomycin. In addition to the reappearance of fever, lymphadenopathy, and the characteristic roentgenologic evidences of miliary disease of the lungs, choroidal tubercles developed in one patient and

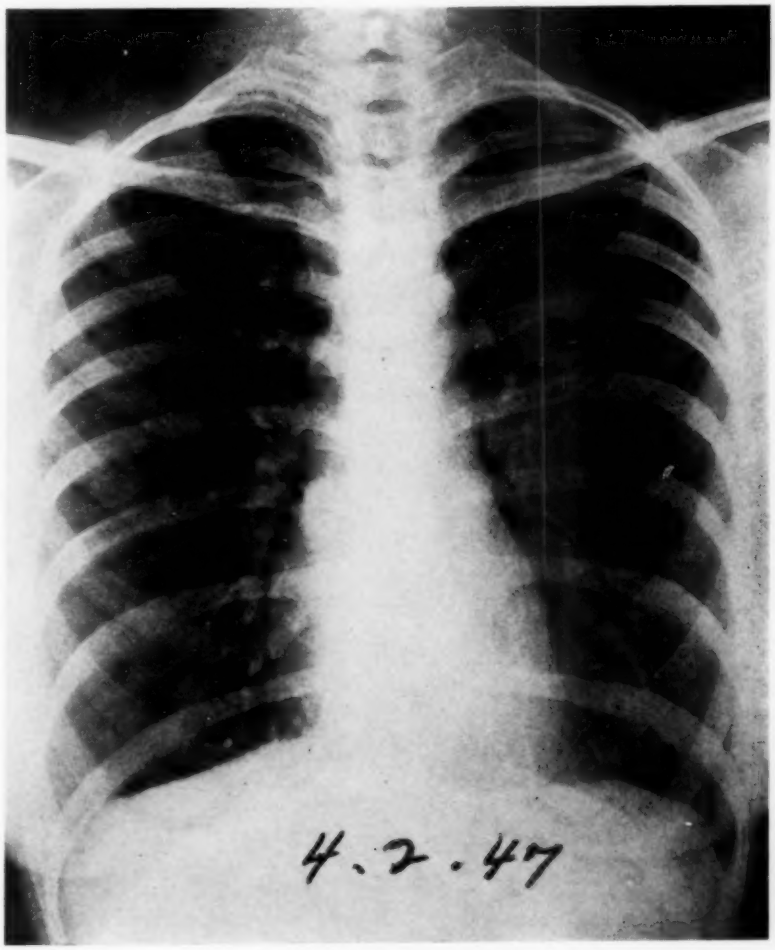

FIG. 6j2.

demonstrable bacteremia in another, despite intensive (three grams daily) streptomycin therapy.

The bacteriologic course of the survivors was in distinct contrast to the findings in the fatal cases. Streptomycin-resistant organisms were never isolated from the five patients who have survived one year after the onset of generalized hematogenous tuberculosis. Moreover, drug-resistant bacilli were never obtained from the two patients whose meningitis is in complete

remission five months after the cessation of therapy. Also in this category is the infant whose miliary tuberculosis was completely healed on postmortem examination (vide infra). It should be emphasized, however, that in these seven infections it was not always possible to isolate organisms at any time after the start of treatment, and in no instance were bacilli obtainable later than the sixtieth day of therapy. The remainder of the generalized hema-

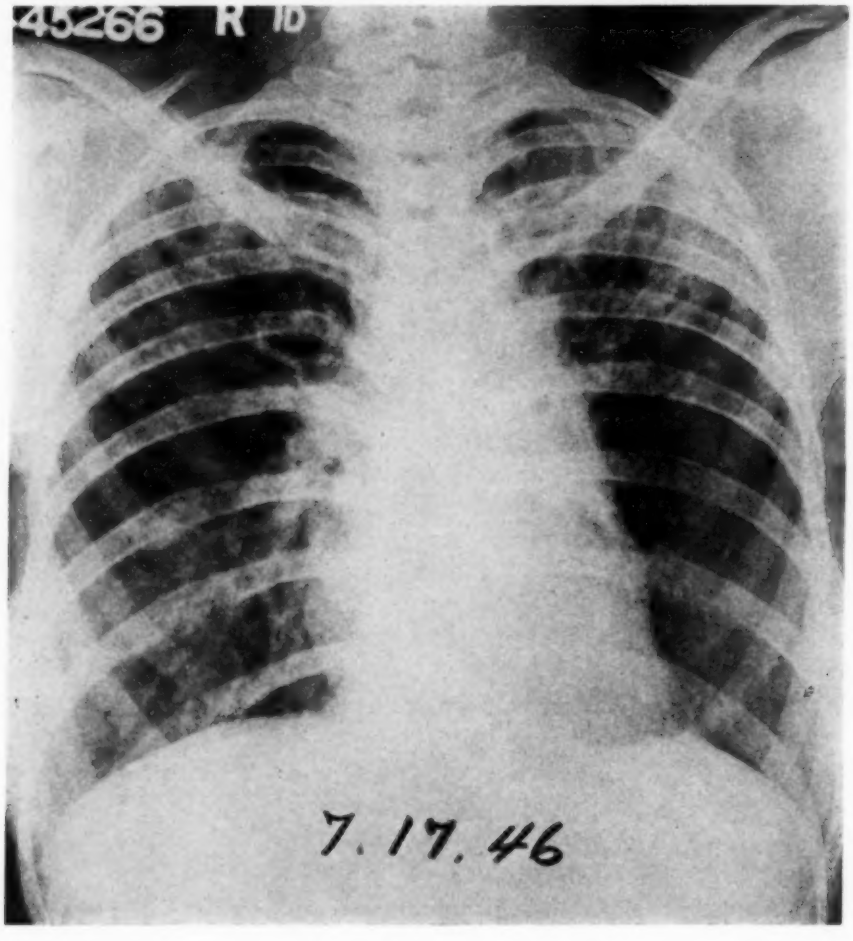

FIG. 6k1.

togenous-meningitis group from whom drug-resistant bacilli were never obtained, consist of three individuals who have completed treatment only recently and the man who died of meningitis on the fortieth day of therapy.

It is of interest that one of the five 12-month survivors, from whom drug-resistant bacilli were never obtained, developed clinical evidences of active tuberculosis two and a half months after the cessation of therapy. Tubercle bacilli could not be cultured from the patient at the time of the

relapse, and the latter appeared to respond satisfactorily to a second course of antimicrobial therapy.

In summary: fatal miliary tuberculosis appeared in all four individuals (with previous miliary disease), from whom drug-resistant bacilli were isolated. Conversely, drug-resistant bacilli were never isolated from the patients with generalized hematogenous tuberculosis or meningitis who eventually attained satisfactory remissions.

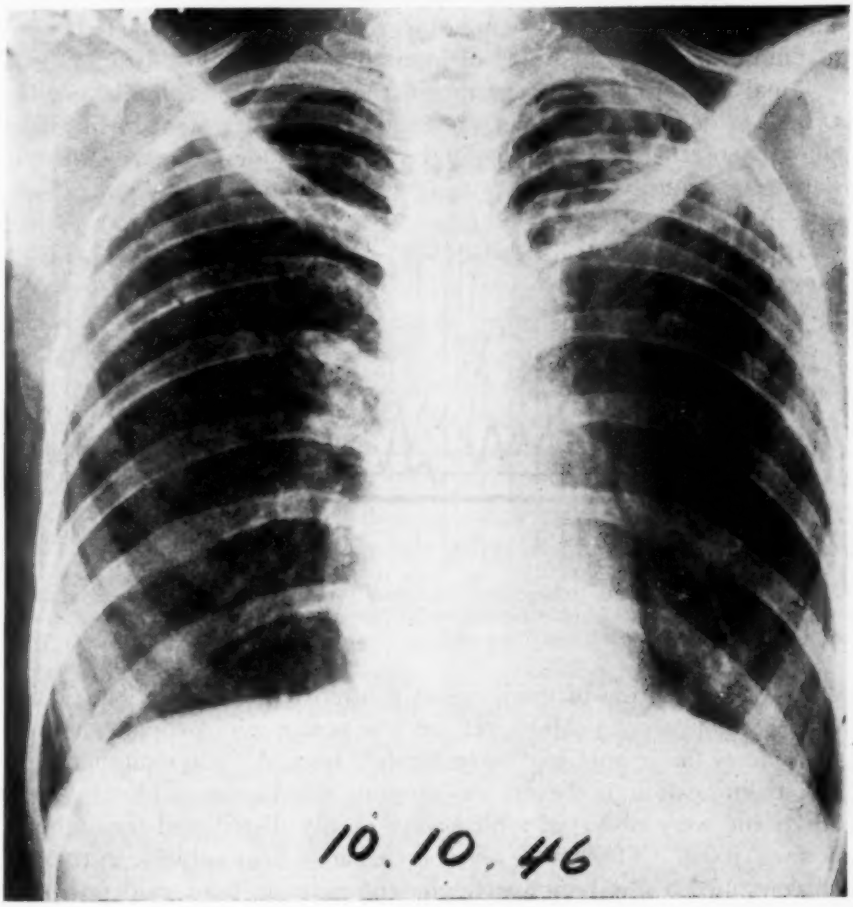

FIG. 6k2.

Histopathologic Observations. Postmortem examinations were obtained in six of the seven fatal cases of acute miliary tuberculosis. Two of the patients had experienced only short-lived periods of improvement and had had actively progressing infections associated with streptomycin-resistant bacilli for 30 to 60 days before death. In both cases gross and microscopic examination of the tissues revealed the characteristic changes of tuberculosis. It was not possible to detect histologic traces of the considerable although

temporary regression of the process in the lungs which had occurred several months previously.

Definite evidences of healing were revealed, however, on investigation of the tissues of the patients who had experienced virtually complete remissions at some time during therapy. Moreover, there was evidence of modification of the pulmonary lesions in the tissues of the man who died of meningitis after only 40 days of streptomycin therapy. A detailed description of these findings will be published elsewhere.[16]

The most striking changes were observed in the lungs of the two year old infant (figure 6a) who had died of internal hydrocephalus, 10 months after the original institution of streptomycin therapy for acute miliary tuberculosis. All evidence of the miliary infection had disappeared during the first few months of therapy, and had never returned despite the development of relapsing meningitis.

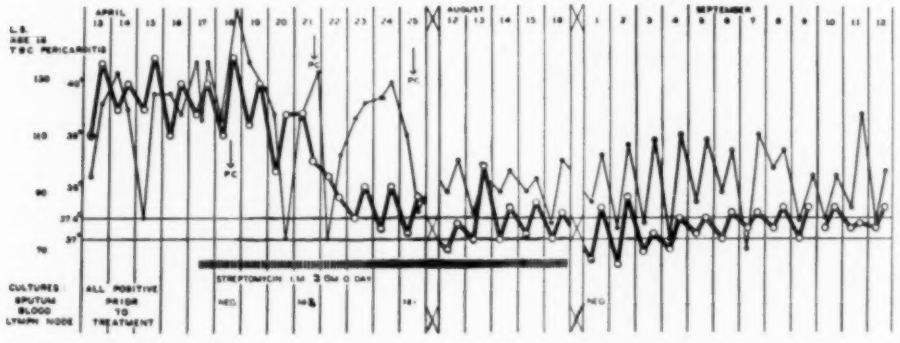

FIG. 7. Patient L. St., tuberculous pericarditis with effusion. Note abrupt defervescence after administration of streptomycin. Vertical arrows indicate pericardeses performed to obtain fluid for streptomycin assays.

On gross inspection of the lungs at postmortem examination, no abnormalities were apparent. Moreover, on low power microscopic examination, the pulmonary tissue appeared to be entirely normal. On examination with greater magnification, however, tiny circumscribed areas of loosely arranged fibrous tissue were observed which were evenly distributed throughout the pulmonary tissue. There were no tubercle bacilli demonstrable in these areas which contained a few lymphocytes but no giant cells or evidence of acute inflammation. In fact, it was impossible to identify the lesions as tuberculous, although they presumably represented the end stage of the miliary tuberculosis which had been demonstrable by roentgenologic and bacteriologic examinations 10 months previously.

A different type of lesion was present in the lungs of a patient who had presented the diphasic type of course described previously. In conformity with the roentgenologic examinations obtained shortly before death, the lungs at post mortem were studded with tubercles. In contrast to characteristic miliary tubercles, however, the lesions observed consisted of three

distinct zones. In the majority of the lesions there was an inner zone of necrotic tissue which was surrounded in whole or in part by a definite ring of fibrous tissue. Outside the ring of fibrous tissue, there was a third ring of active cellular inflammation in which tubercle bacilli were present. Thus it appeared as if partially healed tubercles had broken down to form newly active disease.

Skin Sensitivity to Tuberculoprotein. Intracutaneous skin tests (Mantoux) were made at approximately monthly intervals with old tuberculin; 0.001 mg. was given as the first dose and the test repeated with tenfold increases up to 1.0 mg. when necessary. No consistent or significant changes in the degree of sensitivity were noted during or after the streptomycin treatment, except in one case. This patient (figure 6a) with miliary tuberculosis and meningitis, whose generalized systemic infection was apparently cured but who died of hydrocephalus, became negative to doses as high as 2.0 mg.

Toxicity. Observations on the toxic effects of the streptomycin regimen in use in this series were made and are presented in detail elsewhere.[7, 10, 14] It is sufficient to state here that all of the important manifestations of toxicity which have been noted following the use of partially purified preparations of streptomycin were also encountered following the use of the highly purified material administered in three gram daily doses.

Discussion

On the basis of the observations which have been presented, it appears that streptomycin exerts a striking effect upon the course of generalized hematogenous and meningeal tuberculosis. The results are thus in complete agreement with the observations previously reported by Hinshaw and Feldman.[3, 4]

In the present study, evidence of therapeutic activity is afforded by: (1) the uniformity with which the administration of streptomycin was accompanied by marked clinical and roentgenologic improvement; (2) the disappearance of tubercle bacilli from those discharges in which they had been easily demonstrable before therapy; and (3) an impressive degree of healing of the lesions in the lung, as revealed by histologic examination.

Six adults with bacteriologically proved meningitis, miliary, or other generalized hematogenous forms of tuberculosis are in complete remission five to 12 months after the cessation of streptomycin therapy. A seventh individual, though not entirely well, is alive one year after acute miliary tuberculosis and is apparently recovering.

Spontaneous recovery in miliary tuberculosis and in tuberculous meningitis is distinctly unusual. The incidence of apparent recovery reported by Hinshaw and Feldman and encountered in this study is unprecedented and is presumably attributable to the action of the streptomycin.

In contrast to the satisfactory outcome observed in these seven individuals, in another group of seven with miliary tuberculosis, six have died

as a result of their disease and the seventh is not expected to recover. The several months' period of improvement, which appeared soon after the start of streptomycin therapy, was equally striking in both groups. Thus the antimicrobial therapy of tuberculosis is essentially similar to the chemotherapy of other infections. The institution of treatment results in a remission of the infection, permanent in some instances, but followed by relapse in others if the host is unable to maintain control of the infection once antimicrobial action has been withdrawn or ceases to be effective.

In the present study, it appears that the immediate causes of therapeutic failure were the development of drug-resistant strains of tubercle bacilli in four cases and the appearance of meningitis in two.

The fact that tubercle bacilli can be streptomycin-resistant in vivo as well as in vitro has been established in experimentally infected animals by Feldman et al.,[17] by Youmans and Williston [18] and by Steenken and Wolinsky.[19] These investigators observed, in guinea pigs and in mice, that organisms obtained from treated patients and resistant to streptomycin in vitro produced an infection which was uninfluenced by the administration of the drug. It would be difficult to detect the presence of a similar phenomenon in most forms of tuberculosis in humans because of the strong tendency toward natural regression of the infection. In miliary and meningeal tuberculosis, however, the tendency for spontaneous healing is so slight that the development of drug-resistance in vivo should be readily apparent if it occurred before the infection was completely controlled by the host. Evidence for this hypothesis is afforded by the course of the patients with relapsing miliary tuberculosis.

In support of the assumption that these four infections were drug-resistant in vivo are the following observations: (1) During the first 30 to 90 days of streptomycin treatment, there was an hitherto unprecedented regression which presumably represented an effect of the antimicrobial therapy; (2) Despite the continued administration of the drug, however, there was a reappearance of all of the clinical, roentgenologic and bacteriologic evidences of miliary tuberculosis in four instances, and a similar relapse 17 days after the cessation of therapy in a fifth individual. During relapse, a fresh dissemination of organisms occurred under therapy in at least two patients, as shown by the appearance of bacteremia and choroidal tubercles; (3) Unlike the course displayed in the early phases of treatment, all four of the second bouts of miliary tuberculosis were completely uninfluenced by streptomycin and steadily progressed to a fatal termination; (4) At postmortem examination, bacilli obtained from the lesions were as resistant to streptomycin in vitro as the organisms cultured during life; (5) The appearance of relapse coincided in time with the appearance of tubercle bacilli which were highly resistant to the action of streptomycin in vitro; (6) Conversely, drug-resistant bacilli were never obtained from the seven individuals who recovered from meningeal, miliary or other forms of generalized hematogenous infections.

In generalized hematogenous tuberculosis, the organisms are so uniformly distributed through the host that bacilli obtained from most of the available sources should be representative of the entire bacterial population. It is conceivable, however, that in occasional instances there will be foci of organisms which have been exposed to appreciably higher or lower concentrations of a drug than is the case for the bacterial population as a whole. In the present study, there were two instances in which bacilli which were sensitive to streptomycin in vitro were isolated from the cerebrospinal fluid of individuals who were discharging drug-resistant organisms from other lesions. It is possible that these organisms had remained drug-sensitive within the central nervous system because they had received so little exposure to the drug in the absence of intrathecal administration. Except for infected cerebrospinal fluid, it would not be anticipated that organisms from such "localized" populations would be obtainable for in vitro testing. It is probable, therefore, both in miliary and pulmonary tuberculosis, that the bacilli discharged by the host (cerebrospinal fluid excepted) usually constitute representative samples of the bacterial population within the body.

Even if a particular culture represents a fair sample, however, it is usually tested in vitro under conditions which favor the growth of only those cells which are resistant to streptomycin. Thus, if only a fraction of the cells of a culture are drug-resistant, the entire culture might appear to be resistant when tested in liquid media. It is not believed that this phenomenon played a significant rôle in the streptomycin-resistance studies of the present investigation. The rate at which the streptomycin-resistant inocula grew, and a few isolated tests in solid media, both indicate that most, if not all, of the cells were streptomycin-resistant in the so-called resistant cultures.

It should also be noted that it is possible to alter the value for the streptomycin-sensitivity of a particular culture by appropriate alterations in the conditions of the test. In the technic used in the present experiments, the concentrations of albumin (0.5 per cent) and of Tween (0.02 per cent) are of the utmost importance. Fisher [20] has recently observed that, in a less rich medium with a low concentration of albumin (0.2 per cent) and a high concentration of Tween (0.05 per cent), falsely low values for the streptomycin sensitivity of tubercle bacilli may be obtained. This albumin-Tween effect is not observed under the conditions of the test employed in this investigation.

The mechanisms by which microörganisms develop resistance to antimicrobial agents are poorly understood.[21] It is possible that there is no unitary explanation of the phenomena, but that several different types of mechanism may be operative. Regardless of which of the currently held explanations of the phenomenon may be correct, it would seem that streptomycin-sensitive bacteria will eventually become streptomycin-resistant if they are continuously or repeatedly exposed to the drug in a situation in which complete healing or arrest of the lesion fails to occur. It is by no means clear whether the bacteria which remain within the host after ap-

parent arrest of the lesions also become drug-resistant, but there is reason to believe that they may not. In two instances in the present series, lesions which healed under therapy, and hence discharged no demonstrably resistant tubercle bacilli, relapsed three to four months later and were apparently still susceptible to the effects of streptomycin. Moreover, Karlson and Feldman have recently observed,[17] in guinea pigs purposely treated with low doses of streptomycin, that the organisms isolated from grossly healed lesions were sensitive to streptomycin in vitro. In contrast, the tubercle bacilli obtained from macroscopically unhealed lesions were highly resistant to the action of the drug in vitro. In four of the five instances in the present study in which bacilli were obtained after the second month of therapy, the organisms were drug-resistant in vitro. In the fifth case (also a fatality) equivocal results were observed on in vitro testing of the only culture obtainable.

The high incidence of bacterial resistance when unhealed lesions are present for more than a few months of therapy creates a therapeutic dilemma in the treatment of miliary tuberculosis. The goal of antimicrobial therapy is to establish control of an infection for a sufficiently long period to afford opportunity for the host to mobilize mechanisms for permanent control. The very fact that generalized hematogenous tuberculosis becomes established at all indicates either that the usual mechanisms for the localization of tuberculous infection are not operative or that a purulent focus has unusually direct and continuing access to a major vascular channel. In either of these situations, in order to avoid relapse, it would be necessary to maintain antimicrobial therapy for a much longer period than would be required for a process already localized by the host to an area of lung. Thus in the treatment of miliary tuberculosis, it would seem reasonable to continue streptomycin therapy uninterruptedly and for as long as possible. If this procedure is followed, however, relapse with drug-resistant organisms is apt to occur unless a considerable degree of healing occurs during the first few months of treatment. The observations of Miller and Bohnhoff [22] and of Hall and Spink [23] on *Meningococcus* and *B. abortus* are disturbing in this connection for they suggest the possibility that continuation of streptomycin in the presence of drug-resistant organisms might actually enhance the pathogenicity of the latter.

Until more information is available, it seems advisable to choose the lesser of two evils by limiting the period of streptomycin therapy to only six or eight weeks. Although this procedure might increase the chance of post-treatment relapse, it should appreciably decrease the risk of relapse with streptomycin-resistant organisms.

The complication of meningitis which was apparently responsible for two of the failures in therapy presumably arose from foci which were present in the brain before therapy, and which slowly evolved to the point of recognition while the drug was being administered by the intramuscular route. In support of this assumption is the fact that the concentrations of streptomycin attained in the nervous system following intramuscular administration are

notably low. Moreover, it is unlikely that blood-borne metastasis to the brain would occur at the time of the most rapid regression of the other miliary lesions.

The development of meningitis considerably complicates the antimicrobial therapy of any infection, tuberculous or otherwise. It is by no means clear why invasion of the central nervous system by members of a particular bacterial species results in an illness which is so much less amenable to treatment than the infections produced elsewhere by the same organisms. It is unlikely that the phenomenon can be explained wholly if at all on the basis that the various drugs fail to penetrate the central nervous system in sufficient concentration. It seems much more reasonable to believe that the natural mechanisms by which the body destroys tubercle bacilli and certain other bacteria such as pneumococcus, are considerably less efficient within the central nervous system or other body compartments than they are in the lung. It is probable that the natural mechanisms for the removal of necrotic tissue and the repair of diseased areas are also less efficient in the body compartments. Without the operation of these natural mechanisms for the eradication of bacteria, and repair of the lesions, the effectiveness of antimicrobial therapy is considerably impaired. Thus in tuberculous meningitis as in pneumococcus meningitis, there will be a high incidence of therapeutic failure despite the availability of powerful antimicrobial agents.

From the experience in the present series of nine patients, there are indications that the chance of a successful therapeutic result in tuberculous meningitis might be greater when the meningitis is not accompanied by acute generalized hematogenous tuberculosis. When the meningitis arises in association with a generalized infection, there is the possibility of developing a drug-resistant systemic infection which dominates the total illness. Moreover, the chance that multiple foci are present within the brain is much more likely. Conversely, in tuberculous meningitis without generalized hematogenous infection, there is a possibility that only a single focus is concerned, and hence a therapeutically induced remission might be less likely to be followed by relapse.

The rapid defervescence and disappearance of clinical toxicity, which followed the institution of therapy in the majority of the generalized hematogenous infections, was a most striking and provocative phenomenon. At times (figure 4a) the appearance of the phenomenon was so rapid and abrupt as to resemble the crisis of pneumococcus pneumonia. The mechanism by which the phenomenon occurs in tuberculosis is not at all clear. It is generally believed that invasion of unsensitized tissue by *M. tuberculosis* does not produce fever and the other evidences of systemic toxicity.[24] Presumably, these phenomena arise as a consequence of the reaction of previously sensitized tissue to products derived from tubercle bacilli. The products, which are not harmful to human tissue in the absence of prior sensitization, are released from dead organisms and are also elaborated to an unknown extent by living bacilli. So far as is known, streptomycin acts only on the

living tubercle bacilli and is chiefly effective on actively multiplying cells.[25] There is no evidence that the drug reacts with the bacillary products which are presumed to be responsible for the production of clinical toxicity. Nevertheless, the introduction of streptomycin results in a prompt disappearance of the systemic manifestation of toxicity, and the phenomenon occurs despite the persistence of the capacity to react to the particular products of the bacillus used in testing the skin reactions to tuberculoprotein.

It is difficult to explain streptomycin-induced crisis if the principal cause of toxicity, in sensitized individuals, is a product of dead organisms. Even if it be assumed that the drug drastically lowers the bacterial population and thus reduces the number of cells eventually available for autolysis, it would be anticipated that during the period of such a rapid reduction an intensification of toxicity might occur. It seems much more likely that the production of toxicity is directly related to the presence of actively growing bacterial cells. Thus the rapid disappearance of clinical toxicity would be the result of a sudden drug-induced interruption of bacterial growth and multiplication rather than a consequence of the neutralization of autolytic products.

The usual range of the multiplication-time of tubercle bacilli in vivo is not known, and presumably varies considerably with the intensity of the infection. Youmans has found, however, that the usual range of multiplication-time for organisms growing in a liquid synthetic medium is 36 to 72 hours.[26] It is of interest to compare this value with the 72 to 96 hour period required for the disappearance of signs of toxicity in the present series of clinical infections.

The questions raised by this phenomenon of streptomycin-induced crisis have important implications in regard to the pathogenesis of tuberculosis and its relation to antimicrobial therapy. It is to be hoped, therefore, that the subject will receive considerable further investigation.

Another phenomenon worthy of mention is the rapid reduction of the size of the cardiac silhouette during the first two weeks' treatment of three patients with miliary tuberculosis. It is assumed that this phenomenon represented the resorption of a pericardial effusion or the disappearance of a considerable degree of cardiac dilatation. In no instance, however, was there any clinical evidence of the presence of either of these two complications.

From the results of the present investigation, it may be seen that in the streptomycin treatment of generalized hematogenous tuberculosis there are so many unsettled questions which pertain to the parasite or to the host, that it is impossible to outline an ideal chemotherapeutic regimen at this time. The results which have been presented were observed on a regimen of 3.0 grams of streptomycin daily, administered continuously for a period of three or four months. This regimen was chosen arbitrarily in an attempt to afford the maximum therapy, presumed to be compatible with safety, over the longest period of time which would be generally practicable. It is conceivable that the high incidence of one cause of failure, the appearance of

drug-resistant strains of bacilli, might be related to the length of the total period of therapy. At least it can be stated that the appearance of drug-resistance was not prevented by what is, in effect, the maximal tolerated regimen. Accordingly, an investigation of the use of a lower daily dose (one gram) for a period of six to eight weeks is in progress, and will be reported at a later date.

Summary

The administration of streptomycin to 17 patients with bacteriologically proved meningeal, miliary or other types of generalized hematogenous tuberculosis was followed, in every instance, by a striking alteration in the course of the infection. Six of these individuals (meningitis, two; * miliary, two; and other forms of generalized hematogenous disease, two) have attained complete remissions which have been maintained for five to 12 months after the completion of therapy. A seventh patient is apparently recovering one year after an acute miliary infection. Another seven individuals, all with miliary disease, have died as a consequence of their infection. The remaining three patients have only recently completed therapy. Meningitis was present, or appeared during therapy, in seven of 13 patients with miliary tuberculosis, but was the principal cause of death in only two instances. In every one of four patients from whom bacilli resistant to streptomycin in vitro were obtained, the miliary infection resumed a progressive course which terminated fatally despite further streptomycin therapy. Histologic and bacteriologic examination of the tissues of six of the fatal cases revealed changes which could be correlated with the clinical, bacteriologic and roentgenologic status of the infections at the time of death.

Conclusions

1. In meningeal and generalized hematogenous tuberculosis, the administration of streptomycin results in a remission of the infection, permanent in some instances, but followed by relapse in others when the antimicrobial action is no longer exerted.

2. In generalized hematogenous tuberculosis, the appearance of tubercle bacilli which are resistant to the action of streptomycin in vitro reflects the presence of a drug-resistant infection in vivo.

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* One of these patients has developed a clinical and bacteriologic relapse since the printing of this report.

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CASE REPORTS

PRIMARY CARCINOMA OF THE GALL-BLADDER IN A PATIENT WITH CONGENITAL HEMOLYTIC JAUNDICE*

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Introduction

Congenital hemolytic jaundice and primary carcinoma of the gall-bladder are both relatively rare diseases. The occurrence of the two in our patient was probably not a mere coincidence—the former condition was undoubtedly indirectly responsible for the later fatal disease. It was because of this probable etiological sequence of events (congenital hemolytic jaundice → cholelithiasis at an early age → primary carcinoma of the gall-bladder and death at 36 years of age) that we are reporting this unusual case.

Case Report

A white, 36 year old coast guardsman was admitted to the U. S. Marine Hospital, Kirkwood, Missouri, on October 16, 1945, with the complaints of weakness, loss of weight, loss of appetite and slight upper abdominal pain of one month's duration.

Present Illness. During the latter part of August, 1945 the patient began to feel weak. During September, 1945 he did not feel up to par but had no localized complaints. On October 7, 1945, while home on leave, he developed fever, nausea, anorexia, and marked weakness. He had lost about 30 pounds. He went to bed and remained there for seven days, when he reported to the medical officer and was ordered to the hospital.

Family History. Father died accidently. Mother and sister well. There was no history of blood dyscrasia in the family.

Past History. He had served in the South Pacific for two years until April, 1945. Typhoid fever at age twelve. In June, 1933 he had a splenectomy for congenital hemolytic jaundice of eight years' duration.‡ The removed spleen was four times normal size and showed increased fibrosis and hyperplastic splenitis. At this operation the gall-bladder was noted to contain many small stones. Six months postoperatively he was apparently well. The jaundice had disappeared, as evidenced by the Van den Bergh reaction which was positive indirect, 0.28 mg. per cent. The red cells still showed slightly increased fragility.

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† At the time this article was written both authors were on active duty in the Reserve Corps of the United States Public Health Service. This article was approved for publication by the Surgeon General of the USPHS.

‡ We wish to thank Dr. G. O. Broun, Medical Director of Firmin Desloge Hospital, for allowing us to review in detail the record of our patient's hospitalization in 1933 at that institution.

Physical Examination. The patient was 66 inches in height and weighed 137½ pounds. The temperature on admission was 101° F., the pulse rate was 100, and the blood pressure was 110 mm. Hg systolic and 70 diastolic. He was a young white male who appeared slightly jaundiced. There was a slight icteric tinge of the sclerae. The abdomen was rounded and soft. There was a large curved, well healed scar on the left side of the abdomen. There was slight tenderness in the right upper quadrant, and the liver edge was palpable 2 cm. below the costal margin. Otherwise, the examination was negative. A tentative diagnosis of catarrhal jaundice was made.

Laboratory Studies. The hemoglobin was 85 per cent; the red cell count was 4,160,000, and the white cell count was 15,000. The differential count was normal, showing 72 per cent neutrophiles. Repeated urinalyses were negative except for a trace of albumin. The icteric index was 6.6 and 6.0 on consecutive days. The blood sedimentation rate was greatly increased, reaching 23.5 mm. in 20 minutes. Blood culture was reported negative on October 20 and was again negative on October 25. Agglutination tests were reported negative for *B. abortus, P. tularensis* and *S. paratyphi A.* Agglutination was obtained with *E. typhosa* antigen in 1:80 dilution and with *S. paratyphi B* antigen in 1:160 dilution. Stool examinations were negative for parasites, and the culture produced *E. coli.* The red cell fragility range was .471 to .300 with a method which gives a normal range of .412 to .300. Roentgen-ray examination of the chest was entirely negative. The cholecystogram showed numerous small gall stones but no evidence of filling of the gall-bladder with the dye.

Clinical Course During Preoperative Period. The patient had a continued fever ranging from 100 to 103.6° F. He evidenced very little distress except for malaise and slight soreness in the right upper quadrant. The initial diagnosis was ruled out by the normal icteric index. He had received booster shots for typhoid and paratyphoid every year for three years, and so the positive agglutination tests were not thought to be significant. A tentative diagnosis of abdominal Hodgkin's disease was made. On October 25, because infection could not be ruled out, and because the white cell count had risen to 25,000, he was started on 50,000 unit doses of penicillin every three hours. It was discontinued on November 1, 1945. There had been no effect upon the patient's general condition nor upon the temperature range. On this day there was slight tenderness in the right upper quadrant, and the liver was palpable 3 cm. below the costal margin. There appeared to be a rounded irregularity of the liver edge. A sternal biopsy was obtained which showed large clumps of normally cellular marrow. There was a normal distribution of erythroid and myeloid elements, but some of the myelocytes showed toxic granules, and there was a slight shift to younger forms. The findings were thought to be compatible with a chronic infection or a chronic disease such as Hodgkin's disease.

The fever continued, varying from 101 to 104°. The white cell count rose to 32,000 while the hemoglobin fell to 60 per cent and the red cell count to 3,900,000. There were no further symptoms, nor were there any further physical findings except for progressive loss of weight and strength.

Operation. Exploratory laparotomy was done on December 3, 1945, using continuous spinal anesthesia. The peritoneal cavity contained a large amount of clear amber fluid. The gall-bladder was thickened and indurated, under great tension, and almost completely surrounded by omental adhesions. The liver was enlarged and studded with innumerable nodules varying in size from 1 mm. to 2 cm. These nodules were hard, of a pale yellowish color, and had the gross appearance of carcinoma. No further extensions were found. The spleen was absent, and there were numerous adhesions at its former site. When the gall-bladder was opened, approximately 200 black gall stones, varying in size from 5 mm. to 1 cm., were found and removed. At one point the gall-bladder had perforated into the liver. A friable, cauliflower-like growth involved the gall-bladder mucosa. A section of the fundus

of the gall-bladder was removed for histologic study, and a drain was sewn into the gall-bladder. A liver biopsy was obtained.

Histopathologic Report. The liver was practically replaced by large pale staining cells with large nucleoli, well defined nuclear membranes, and polyhedral cytoplasm. Mitoses were frequent. There was no differentiation as to histogenic structure, except that there was some attempt at adenomatous formation. The adjoining liver cells showed extreme atrophy and congestion of the sinusoids. There was considerable deposit of pigment in the Kupffer cells. The gall-bladder wall showed extreme hyalinization, and in one small area the same type tumor as was found in the liver was present.

Diagnosis. Carcinoma of the gall-bladder and liver, chronic cholecystitis, and cholelithiasis.

Postoperative Course. Following operation the temperature chart continued to show the same type and degree of elevation as before operation. Large quantities of ascitic fluid drained for several days, but at no time did bile appear on the dressings. The wound healed well, and the drain and sutures were removed on the ninth day. Jaundice became evident a few days after operation and increased rapidly. Edema of the lower extremities and dependent portions of the trunk developed on the fifteenth day. He gradually became weaker and died at 12:20 p.m. on January 4, 1946, 32 days after operation.

Autopsy. Autopsy was done at 3:30 p.m., January 4, 1946. The principal finding was primary carcinoma of the gall-bladder with massive metastases in the liver, especially in the right lobe. There was no evidence of pulmonary disease or metastases. There was a large amount of free fluid in the thorax and the peritoneal cavity. No evidence of carcinoma was found in any portion of the body except in the gall-bladder, the liver, and the adherent omentum. Microscopic examination of the tissues revealed epidermoid carcinoma.

Review of Literature

The incidence of gall stones in congenital hemolytic jaundice listed in several standard texts of hematology [1] has been variously estimated from 60 to 70 per cent of cases. Gall stones occur at a much younger age in people with this condition than in the general population and many instances of cholelithiasis in early childhood have been reported.[2]

Estimates of the percentage of the general population that have cholelithiasis would be very speculative since "gall stone surveys" of large representative sections of our population have never been made. The incidence has been suggested to be somewhere between 10 and 20 per cent of adults [3]—definitely higher in females.

Thus the incidence of gall stones is three to six times higher in congenital hemolytic jaundice than in the population as a whole, and gall stones appear at a much earlier age.

The exact rôle of gall stones in the etiology of primary carcinoma of the gall-bladder is still obscure. Ewing [4] in reviewing the literature, quotes several authors who found cholelithiasis in 70 to 100 per cent of cases of primary carcinoma of the gall-bladder. He considered the remarkable etiological relation with cholelithiasis as one of the most interesting features of the disease.

While experimental evidence is definitely lacking [5] the consensus of contemporary clinicians was expressed by Bockus [3] in the following statement: "Statistical studies suggest that antecedent calculous cholecystitis has an im-

portant relationship to the occurrence of cancer of the gall-bladder." Most pathologists [6] concur with this opinion.

Graham [7] in 1931 was among the first to recommend cholecystectomy in all cases of gall stones—with or without symptoms—to prevent the development of carcinoma. Although all subsequent writers [8] do not agree, the majority of recent papers [9] urge cholecystectomy for almost all calculous gall-bladders as the only means of reducing the incidence and mortality rates for primary carcinoma of the gall-bladder.

Horne [10] recently reported two cases of congenital hemolytic jaundice with non-malignant gall-bladder complications requiring surgical treatment. In reviewing this problem he concluded that cholecystitis and cholelithiasis are frequent complications, and he advised cholecystectomy in all cases of congenital hemolytic jaundice when gall stones are present. This may be done at the time of splenectomy or later.

It is not in the province of this paper to discuss the efficacy of splenectomy in congenital hemolytic jaundice; however, it is of interest to note the following facts in this case. Splenectomy permanently alleviated the jaundice which had been present for about eight years. However, 13 years after splenectomy the increased erythrocyte fragility was still present.

To our knowledge this is the first report of a case of primary carcinoma of the gall-bladder in a case of congenital hemolytic jaundice. It is hoped that this report may stimulate the reporting of any similar cases and that it may possibly help to prevent other patients from developing this rare and fatal complication.

Summary and Conclusions

A case of primary carcinoma of the gall-bladder in a patient with congenital hemolytic jaundice is presented.

The etiological relationship of the two diseases is discussed. Congenital hemolytic jaundice caused gall stones at an early age in our patient. The presence of gall stones for over 12 years was probably a contributing factor in the development of malignancy.

Since non-malignant gall-bladder complications are frequent in patients with congenital hemolytic jaundice, the possibility of developing malignancy is an additional reason for cholecystectomy in these patients when gall stones are present.

Note: We wish to thank Dr. Nathan A. Womack, Dr. Carl V. Moore, and Dr. David E. Smith for their clinical and laboratory studies of the patient.

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THE EARLY DEVELOPMENT OF SYPHILITIC AORTITIS *

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THE clinical diagnosis of aortitis is usually made late in the course of syphilitic infection. Although the literature contains references to its early development, it is not generally appreciated that the condition may sometimes be found within a short time after the primary infection. In the case to be reported symptoms appeared 10 months after infection and death from heart failure occurred 22 months later.

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From the Medical Service, St. Luke's Hospital, Cleveland, Ohio.

Case Report

A colored male, aged 41 years, was seen in the Out-Patient Department October 25, 1944, complaining of dyspnea and orthopnea since August, 1943.

The past history is irrelevant except for the following important information: In 1928, Wassermann and Kahn reactions were negative in this hospital. On October 3, 1942, he received a pre-induction examination at his local draft board. No physical defects were noted and his serology was negative. Three weeks later, October 23, he was sent to the induction center where another physical examination was carried out. There was now a chancre present on the penis and the serology was positive. A careful survey of the heart including a teleroentgenogram revealed no evidence of cardiovascular disease. On account of the presence of infectious syphilis he was rejected for military service and was given heavy metal therapy by his private physician. This consisted of 16 injections of Mapharsen and 10 injections of bismuth with a lapse of several months during the course of arsenical therapy.

Physical Examination. The patient was in obvious respiratory embarrassment. The forceful pulsations of the carotid arteries were readily noticed. The pulse was of typical water-hammer character. The blood pressure was 170 mm. Hg systolic and 70 diastolic. The precordial activity was increased and the point of maximum intensity was in the anterior axillary line. The rhythm was regular. At the base of the heart both systolic and diastolic murmurs were heard. These were to-and-fro in character and of the type that we associate with aortic regurgitation. There were many râles in the chest and slight pitting edema, evidence of congestive failure.

The teleroentgenogram at this time showed an enlargement of the heart in all diameters, predominantly of the left ventricle. The transverse diameter measured 16.5 cm. as compared with the maximum normal of 12.6 cm. and represented an enlargement of more than 25 per cent above the expected normal figure. Mazzini and Wassermann reactions on the blood serum were strongly positive. It was our impression that this represented syphilitic aortitis with an unusually rapid onset. The cardiac status was placed in Class III.

Subsequent Course. The patient was confined to bed and after digitalization he was comfortable enough to leave the hospital on his nineteenth hospital day.

He was followed in the Cardiac and Venereal Disease clinics of this hospital. In December, 1944, weekly injections of bismuth subsalicylate were begun, a course of which was to precede the use of small doses of Mapharsen. He received, from December, 1944, to April, 1945, fourteen injections of bismuth subsalicylate 0.13 gm. Because of the progressively unfavorable course of the disease no Mapharsen was given. In spite of treatment and excellent coöperation on the part of the patient, cardiac failure increased in severity, necessitating many hospital admissions.

The seventh and last admission was on May 20, 1945, the patient having been discharged only six days before. He complained of abdominal pain, some diarrhea, and vomiting. Physical examination showed severe congestive heart failure and, for the first time, jaundice and an enlarged liver. The teleroentgenogram demonstrated a further increase in the size of the heart. The transverse diameter was 18 cm. The blood nonprotein nitrogen was 167 mg. per 100 c.c., and creatinine 3.5 mg. per 100 c.c. Serum icterus index was 50 units. Except for a slight trace of albumin the urine was not remarkable. For a while the failure lessened and concomitant with this there was a drop in the degree of nitrogen retention and icterus. On June 16, 1945, the nonprotein nitrogen was 41.8 mg. per 100 c.c., creatinine 1.2 mg. per 100 c.c., and the icterus index 17 units.

His condition then became worse and in spite of oxygen and other supportive measures he died on June 26, 1945.

Autopsy Examination. The important pathological findings were confined to the cardiovascular system. The heart weighed 640 gm. All chambers were dilated and hypertrophied, the left ventricular wall measuring 17 mm. in thickness. The aortic valve was normal but the circumference of the ring was increased to 9 cm. There were no changes in the mitral, tricuspid, or pulmonic valves. The coronary ostia were patent and the arteries were normal. The aorta showed a diffuse thickening extending to a level just above the celiac axis. The wall in this area was increased to 4 mm. in comparison to 1 mm. in thickness of the abdominal portion. The internal surface of the aorta was corrugated and pitted with many irregular, raised, pearly zones. The microscopic examination confirmed the gross diagnosis of syphilitic aortitis.

Conclusion

In view of the systemic nature of syphilitic infection and the high incidence of aortitis found at autopsy, it is not surprising that signs of aortic involvement occasionally are seen early in the disease. The following reports from the literature will serve to illustrate what may be encountered. Brooks [1] reported rupture of the aorta just above the aortic leaflets in a patient with early secondary syphilis. Blackford and Smith [2] reported a case in which rupture of a gummatous aortic cusp occurred eight months after a positive darkfield primary. Reid [3] has studied a patient in whom aortitis developed three months after the initial infection. Sanford [4] reported the development of an aortic aneurysm in a 20 year old Negro, which resulted in death within two years after the primary infection.

In contrast to these extreme examples, the diagnosis in the average case is made much later. Cole and Usilton [5] found in their Coöperative Clinical Group study of 142 individuals in whom the onset of infection could be determined accurately, three patients in whom the condition had developed within five years. Most frequently the period was from 20 to 30 years after infection. Stokes [6] is of essentially the same opinion, indicating that 45 per cent of syphilitic aortitis is recognized in the second and 30 per cent in the third decade of the disease.

For the most part this is attributed to the fact that the disease lies dormant for many years but it may be that a thorough search for the condition is sometimes delayed until the infection has been present for a considerable period of time. The knowledge that syphilitic aortitis is occasionally encountered shortly after the initial infection may, in some cases, lead to its earlier recognition.

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ERUPTIVE FEVER WITH STOMATITIS AND OPHTHALMIA (STEVENS–JOHNSON) *

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IN their discussion of the erythema multiforme group of dermatoses, Sutton and Sutton [1] listed a subvariety: eruptive fever with stomatitis and ophthalmia, *ectodermose erosive pluriorificielle,* or dermatostomatitis. This syndrome has also been called erythema multiforme of the Stevens-Johnson variety; for it was Stevens and Johnson [2] who in the American literature first proposed the designation of this group as an entity apart from *erythema exudativum multiforme* (Hebra). These authors introduced the disease as "a new eruptive fever associated with stomatitis and ophthalmia." However, similar cases have been described previously by Rendu [3] and Fiessinger and Rendu [4] as "ectodermoses erosives pluriorificielles."

Within two years there were admitted to the general medical service, two patients suffering from disorders that fit the descriptions of Stevens-Johnson's disease. The following are the essential data for each case.

CASE REPORTS

Case 1. A 19 year old white male was admitted to the medical service on February 21, 1944, with the chief complaints of cough and sore throat. For several days the patient suffered from a "cold." Four days prior to admission he began to have chills, fever, and sweats. In addition, he developed a harassing dry cough and sore throat. Aside from aspirin and cough syrup containing codeine, the patient had taken no other medication.

In the past, he had suffered from eczema on his face, neck, and in the antecubital fossae, recurring in the late winter and early spring months. In addition, one sister suffered from eczema.

The physical examination revealed a moderately ill white male, dull and apathetic. Temperature, pulse, and respirations were 104° F., 120, and 26 respectively. His eyes exhibited injection of the conjunctivae and the sclerae with some purulent discharge. His nose was congested, and his throat was intensely inflamed. Examination of the chest revealed a few scattered râles at both bases, but other abnormal signs were lacking. The skin felt hot and dry, and in the antecubital fossae there was evidence of a healed atopic eczema. It was the impression that the patient was suffering from an atypical pneumonia.

The laboratory findings were as follows: Blood count: hemoglobin 14 gm.; white blood cell count 11,500, neutrophiles 76 per cent; lymphocytes 22 per cent; eosinophiles 1 per cent; and monocytes 1 per cent. Examination of the neutrophiles revealed a shift to the left and the presence of marked toxic granulations.

Urinalysis: normal. Chest roentgenogram: normal. Kahn test: negative. Heterophile antibody test: negative. Sedimentation rate: 65 mm. per hour. Throat smear: a few Vincent's organisms and the usual bacterial flora. Smear and culture from the secretion in the eyes: many pus cells present, but no organisms present on smear and culture.

Twenty-four hours later, mouth lesions began to appear. The mucous membranes of the mouth, tongue, and throat were covered with several patches of foul smelling,

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dirty yellowish matter. In addition, there was a thick purulent post-nasal discharge. The picture was not unlike an extensive Vincent's infection. At the same time, a painful red papule appeared on the anterior surface of the glans penis. There were no skin lesions present.

Treatment consisted of sulfadiazine orally and sulfathiazole ointment to the eyes. Supportive therapy, including vitamin administration, was instituted. Improvement was gradual. The temperature returned to normal by lysis on the ninth hospital day, and the patient was asymptomatic by the twenty-second day.

Sensitivity (scratch) tests were performed after the patient had fully recovered. He was found to be strongly allergic to dusts, horse dander, chicken feathers, goose feathers, and sheep dander.

Comment: This was a case of erythema multiforme involving chiefly the mucosa of the mouth, throat, eyes, and skin of the glans penis. The syndrome had as the onset an apparent upper respiratory infection. The allergic background as evidenced by an old eczema and positive skin tests may have played a rôle as an etiologic factor; but, on the other hand, at no time during the disease did the allergy flare up.

Case 2. A 20 year old white male was admitted on December 25, 1945, complaining of burning and discharge from his eyes, soreness in the nose and mouth, and a discharge from the penis. Several days prior to the onset, he had a cold consisting of a slight nasal discharge. On December 20, he noted burning and crusting about his eyes. His gums became tender on the next day and bled on slight trauma. The penile discharge and soreness began December 22. On this date he took three tablets of "Ex-Lax."

The past history and family background were non-contributory. The patient's last sex exposure was alleged to have occurred six weeks prior to admission. Previous venereal disease was denied.

The physical examination revealed a moderately ill white male. Temperature, pulse, and respirations were 100.6° F., 80, and 20. The conjunctivae were injected and a mucopurulent secretion was present. His face appeared flushed and slightly edematous. The nasal mucous membrane was covered with small crusted ulcerations. Similar large necrotic plaques were present on the gums, buccal mucosa, hard and soft palates. The cervical nodes were somewhat enlarged. Except for the genitalia, the remainder of the physical examination was negative. On the tip of the glans there was an ulceration. The glans penis was reddened and covered with a dirty grayish exudate. Thick purulent material could be expressed from the meatus.

Laboratory findings on admission were: Complete blood count: hemoglobin 15.8 grams; white blood cell count 7,100 with 67 per cent neutrophiles, 27 per cent lymphocytes, 5 monocytes, and 1 per cent eosinophiles. Kahn test: negative. Urethral smear: many pus cells with Gram negative intra- and extracellular diplococci. Cultures were positive for gonococci. Conjunctival smear; many pus cells present with an occasional cell containing Gram negative diplococci. The appearance was that of a Neisserian infection, but could not be identified with certainty, for cultures revealed no growth. Smear of the mouth and throat: mixed bacterial flora and Vincent's organisms. Blood cultures were not taken.

Treatment with penicillin was instituted in dosage of 20,000 units every three hours by the intramuscular route. Five per cent sulfathiazole ointment was used in the eyes. Attention was also given to oral hygiene. Vitamins were administered in large doses. Within 24 hours the patient was afebrile. The urethral discharge had disappeared, and the secretion from the eyes lost its purulent character. Microscopic examination of the urethral smear revealed the disappearance of the gonococci and a

lessening of the number of pus cells. By the fifth hospital day the balanitis had almost cleared; the conjunctivitis was receding rapidly; but the lesions in the mouth and throat remained unchanged. In addition, ulcers were appearing on the margins of the tongue. On the anterior aspects of the legs and extensor surfaces of the arms there were small reddish maculopapules averaging one centimeter in diameter. Some were hemorrhagic, whereas others developed small vesicles in the center. On the seventh hospital day his mouth began to heal, the balanitis and the conjunctivitis had disappeared, and no new skin lesions had appeared. By January 8, twenty days after the onset of the conjunctival discharge, the patient was asymptomatic. Penicillin, given for the first 11 days, totalled 1,760,000 units.

Comment: This was a mild case of dermatostomatitis. Again, prior to the onset, the patient had a mild upper respiratory infection. The ingestion of the laxative containing phenolphthalein occurred after the onset of the disease. The possibility was suggested that the picture was one of a widespread gonococcal infection as described by Keil.[5] However, the type of mouth lesions were not those seen in Neisserian infections. Gonococcal stomatitis has been reported in the newborn.[1] Probably the patient harbored the organisms, which in turn were activated by the erythema multiforme. This is comparable to those cases wherein secondary infections occur with pyogenic organisms.

Discussion

Although they are included in the category of erythema multiforme, cases of dermatostomatitis exhibit distinctive clinical courses. Cases have been reported by Stevens and Johnson,[2] Ginandes,[6] Klauder,[7] Ageloff,[8] Ellis,[9] Murphy,[10] and Kove.[11] The disease usually attacks children and young adult males. The onset is rather acute, with the appearance of a conjunctivitis and bullous lesions on the mucosa of the mouth and nose. Often vesicular or ulcerative lesions appear on the penis. The anus may likewise be involved. Constitutional symptoms are frequently present, are severe, and associated with high fever and moderate to marked toxicity. The mouth becomes filled with ulcerations covered with dirty necrotic exudate. A few days after onset cutaneous lesions may appear. They range from maculo-papules to bullae. If complications are averted, healing begins in about one week with remission in the constitutional symptoms and is complete in from three to six weeks. However, secondary infections with pyogenic bacteria often occur, affecting chiefly the eyes, producing a purulent conjunctivitis and corneal involvement. A panophthalmitis may subsequently lead to blindness.[2, 6] During the course of the disease laboratory examinations of blood and urine are not characteristic.

The diagnosis is often confused with various types of stomatitis and especially with that due to Vincent's organisms. Conjunctivitis from different causes, venereal diseases, reactions of sensitivity to various drugs, and some of the infectious exanthemata enter into the differential diagnosis. In fact, the patient may first seek aid from a dentist, ophthalmologist, or urologist. However, the course of the disease and the definite association of conjunctivitis and stomatitis, with cutaneous and genital lesions, are very suggestive.

Death may occur as a result of secondary sepsis or toxemia with extensive involvement. From cases designated as erythema exudativum multiforme with stomatitis and ophthalmia the pathology has previously been reported by Edgar and Syverton[12] and Fletcher and Harris.[13]

The treatment of the Stevens-Johnson syndrome is non-specific. Scrupulous oral hygiene is necessary. The eyes should be irrigated frequently if secretion is present. Cutaneous lesions may be treated by local applications when necessary. Because of the soreness of the mouth, feeding is a problem. The patient should be served a liquid or soft diet of high caloric content. Citrus fruits and vinegar are usually too irritating. Supplementary vitamin intake is necessary. Parenteral therapy may be required to combat toxicity and supplement the fluid and nutrient intake.

Secondary infection may lead to a prolonged convalescence, total disability, or a fatal outcome. With the relatively new therapeutic weapons, complications can be averted or treated if they occur. The first case was given sulfadiazine by mouth and sulfathiazole ointment on the eyes. In the second case, penicillin was administered by the parenteral route and sulfathiazole ointment locally for the eyes. Although this patient was moderately ill, the clearance of the secondary infection was prompt. Penicillin has the further advantage of eliminating the Vincent's organisms, which may aggravate the stomatitis already present. It is doubtful that penicillin is specific for dermatostomatitis; for in the patient treated with the drug, the skin and mouth lesions continued to appear and ran their usual courses.

The etiology of this symptom-complex remains unknown. It is doubtful whether any one etiologic factor can be designated as the primary agent in any given case. In each of the patients reported in the article the onset was preceded by an upper respiratory infection; drugs could not be implicated. A similar onset has been cited by Klauder,[7] Rosenberg and Rosenberg,[14] and Edgar and Syverton.[12] Drugs acted as predisposing factors in other patients. Ellis [9] reported one case following the use of phenytoin sodium, and Fletcher and Harris [13] presented two resulting from ingestion of sulfadiazine and Fowler's solution. The resemblance to foot and mouth disease in humans has been emphasized by Klauder,[7] but this could not be proved in the laboratory. A case following the onset of mumps was reported by Kove.[11] Inoculations of various laboratory animals with fluid from the cutaneous blebs failed to produce any positive findings.[12, 15] The possibility of a state of hypersensitivity is suggested by the reactions of the skin and mucous membranes to either drug ingestions or infection.

There exists disagreement as to whether Stevens-Johnson's disease is a clinical entity. This fact further confuses the search for the causative factor; for the same disease may be reported in the literature as Stevens-Johnson's disease or as a variant of *erythema exudativum multiforme*. Stevens and Johnson [2] and Ginandes [6] presented arguments in favor of the syndrome as a separate disease. On the other hand, Klauder [7] and Keil [16] take the opposite view. It appears from the findings of various predisposing factors that eruptive fever with stomatitis and ophthalmia should be listed as a subgroup of erythema multiforme. As Keil [16] points out, mucous membrane lesions actually occur in many patients with erythema multiforme, contrary to opinions of earlier authors. Further, cases have been reported as Vincent's infection with erythema multiforme,[17, 18] conjunctivitis with cutaneous concomitants,[15, 19] or mucosal lesions without dermatitis.[20] The conclusion is that Stevens-Johnson's disease is a variant of *erythema exudativum multiforme*. However, in view of the clinical similarity of various cases, the retention of the name offers the physician considerable information as to the prognosis and therapeutic approach.

Summary

Two cases of erythema multiforme of the Stevens-Johnson variety have been reported. In one patient there appeared to be secondary invasion by gonococci from possibly a latent urethritis. Penicillin treatment over a period of several days checked the secondary infection without altering the course of the dermatostomatitis.

A brief discussion of the etiologic factors is presented. No single factor could be pointed out as the cause of Stevens-Johnson's disease.

Doubt is registered as to whether the disease is in itself a clinical entity.

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EDITORIAL

A PRELIMINARY NOTE ON AN INTERESTING EXPERIMENT

On April 15, 1934, as an aid to the promotion of clinical research in this country, the Board of Regents established the "Research Fellowship of the American College of Physicians." This fellowship, on recommendation of the Committee on Fellowships and Awards, was given each year from 1934 to 1943—when war interrupted the program—to a varying number of suitably promising candidates, no single one ever holding it for more than a period of 12 months.

The Committee on Fellowships and Awards, first called the Committee on the John Phillips Memorial Prize, was established in 1929 as a committee of five with its membership appointed by the President. The President was given free hand in regard to the composition of the committee except that not less than two or more than three of its members could be re-appointed in any year. This device was evidently employed to prevent stagnation within the committee and to ensure a continued influx of new ideas.

The Committee, too, was given free hand; one of its important aims after 1934 was to develop the fellowship as a project which might come to play an increasingly distinctive part in the work of the College. With this idea in mind, while the Board of Regents made the appointments technically, the Committee was authorized to nominate the successful candidate or candidates each year, after combing them from a carefully censored list obtained through communicating with the professors of medicine and pediatrics in the country, with the officers and regents of the College, and with the National Research Council. The last agency was inserted so that nominations might be obtained from this source in case the professors of medicine and pediatrics and the officers and regents were unable to suggest any young men or women of sufficient promise. And finally, in order to systematize its work, the Committee adopted an application form of the general type developed by the National Research Council; in this way the necessary biographical data and attainments of each candidate were recorded in a manner that was uniform and of proved usefulness.

Up to the beginning of the war, 16 fellows had been appointed in this fashion. While their number is small and the possible years of follow-up on their careers are few, yet it has seemed worth while to attempt to evaluate their work. One might argue that if, on the whole, the holders of such fellowships had by now succeeded in accomplishing demonstrably satisfactory results in research, the continuance of such appointments was justified; if not, the funds of the College allocated for their maintenance might, perhaps, be used to better advantage for some other purpose.

The policy of the Committee during the period under consideration was relatively fixed: all Research Fellows were young and were men of reliable

character; they were graduates of different medical schools; and they were chosen a few years after completion of their medical course because already they had exhibited a talent and liking for research or at least had displayed more than normal curiosity as interns or residents in attempting to solve the riddles of clinical medicine. Also, they were chosen, in part, because they needed the financial aid from the stipend attached to the fellowship.

TABLE I

The Age of the Research Fellows When They Were Appointed and Their Medical Schools

Name	Medical School	Year of Graduation	Year of Appointment as Fellow	Age at Time of Appointment
W. R. A.	Ohio State	1938	1941	31
W. W. B.	Harvard	1935	1940	30
L. D.	Harvard	1936	1940	30
A. M. H.	Johns Hopkins	1934	1937	26
C. G. H.	Wisconsin	1940	1942	29
J. H.	California	1939	1942	32
F. K.	Harvard	1931	1934	28
M. J. L.	Rochester	1934	1935	24
H. M.	So. California	1938	1939	26
M. P.	California	1933	1936	28
R. W. R.	Northwestern	1938	1941	33
H. S.	Oklahoma	1936	1940	29
J. R. S.	Washington Univ.	1934	1938	29
M. T.	Yale	1936	1940	31
R. H. W.	Johns Hopkins	1934	1939	30
R. W. W.	Harvard	1933	1937	31

Of the 16 men involved in this study, four were Harvard graduates, two were from Johns Hopkins, two were from the University of California, and the rest were from scattered schools. That half were graduates of only three schools appears to be fortuitous. As a composite group they averaged 29 years in age when they received the appointment and were about three years out of medical school.

By tradition, the Committee has required information as to where each prospective fellow wished to work during the year of his appointment and on what kind of problem, as well as reassurance that were he to receive a fellowship he would be welcome to work in the clinic or laboratory of his choice. Three of the fellows finally selected planned to work in England, one in Cairo under Professor Anrep, and one in Buenos Aires under Professor Houssay. The rest, except one, had chosen American University clinics, and of these, Yale was the most popular since three men desired to spend a year at New Haven. The lone exception hoped to improve his knowledge in chemistry by working at the Rockefeller Institute Hospital under Dr. Van Slyke.

This gives a cursory description of what the Fellows were like and their aspirations.

Two criteria were adopted to measure what the Research Fellows have accomplished: the first is bibliographic and the second academic. Their publications, as listed in the Quarterly Cumulative Index Medicus, were tabulated. Since, at the time of preparing this report, no volume of the Index after June 1946 was available, only publications were included which had appeared in 1945 or previously. As judged in this way, these 16 young men, following their introduction to clinical research under the College's auspices, have already contributed more than 200 articles to medical literature. The manner in which this literature has grown is one of its most gratifying features.

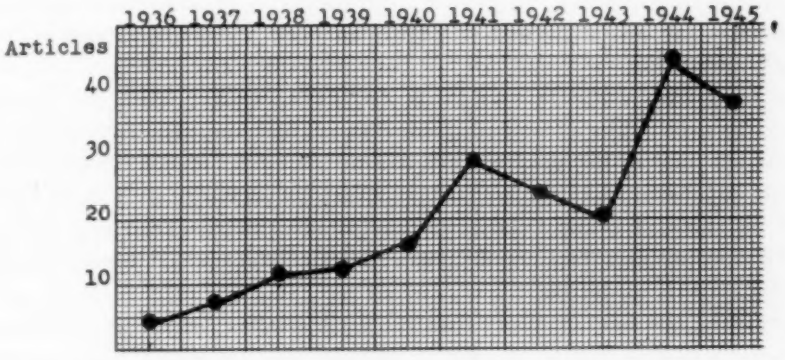

FIG. 1. The printed record in medical periodicals of the Research Fellows.

There has been a rising tide of readable papers flowing from their pens, interrupted during 1942 and 1943 by the war but regaining momentum in 1944 and 1945. This record is impressive. No evidence of mental sterility or laziness has developed amongst the Fellows; rather, once having been exposed to the satisfaction of clinical investigation they have appeared to react as did Dr. Oliver Wendell Holmes when he first came in mental contact with pride of authorship and, like him, they have continued to be productive.

They have written serious papers, as judged by their vehicles of publication. For example, 17 of their articles have been printed in the Annals of Internal Medicine, 17 in the Journal of Clinical Investigation, 13 in the American Heart Journal, 11 in the Journal of Physiology, and almost all of the rest in periodicals of equal respectability or gravity. Occasional—and very readable—reports have been prepared for the benefit of men in general practice and have appeared in various state medical journals. There has been almost no literary padding.

In looking over the titles listed, two striking facts become apparent. The first is the diversity of interests which the Fellows have developed. Most of them have approached clinical research through the disciplines of physiology, chemistry, bacteriology or pharmacology rather than through the more

ancient ones of anatomy or pathology; they have probed almost every corner of medicine with new instruments in an effort to lay bare the fundamentals of disease.

The second reveals the obvious need for team-play in modern clinical research. The majority of investigations which have been described were completed by several men working together rather than by any single individual working alone. Thus it is probable that our Research Fellows have exerted a perceptible influence on their associates, stimulating colleagues to work with them and helping to transfer new ideas and methods from one part of the world to another. Mainly, however, their publications reveal the astonishing complexity of modern clinical research; teams comprising physicists, chemists, surgeons, internists, radiologists, pathologists and bacteriologists are now often needed to pry open even a narrow doorway to new medical knowledge.

As judged by academic standards, the Fellows have made an equally impressive record. The most venerable has scarcely passed his fortieth birthday and yet among the group there are now one professor of medicine, one associate professor, and six assistant professors serving on medical faculties; almost all the rest occupy positions weighted with research or teaching responsibilities; so far, the lure of private practice has proved a poor competitor against scientific ambition.

Certainly, the first crop of Research Fellows has helped to promote clinical research in this country in a way that is gratifying and which has added to the prestige of the College. The question arises as to whether the second

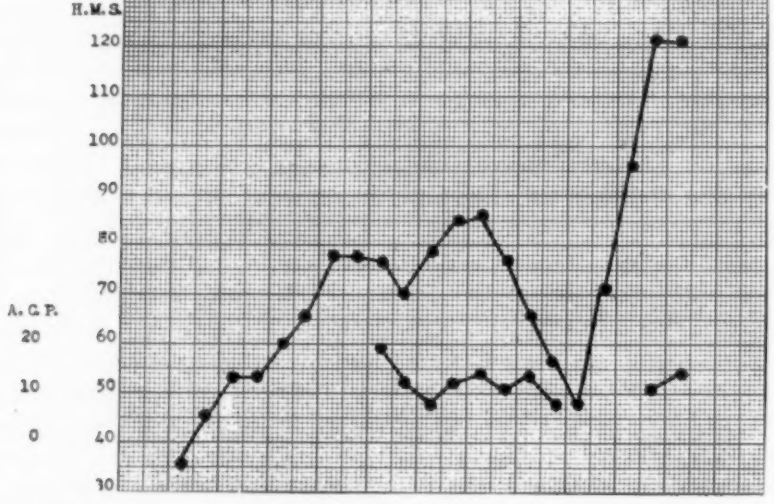

FIG. 2. The apparent growth in research fellowship opportunities. The upper line represents the number of Research Fellows as listed in the Catalogue of the Harvard Medical School year by year. The lower line represents the number of candidates applying for Research Fellowships offered by the College.

crop—which was planted in 1946—can continue to yield so luxuriant a harvest.

Conditions now are far different than they were in 1934; vasts sums of money have been set aside by various foundations or institutions to encourage research fellowships along principles followed by the College, and the number obtainable has increased by leaps and bounds. The accompanying graph was prepared to illustrate what has occurred.

The Harvard Medical School was selected as an example because its catalogues happened to be easily available. Presumably, the experience of Harvard is not unique; about 20 years ago funds for research began to become available from a variety of sources and in increasing amounts, so that the number of individuals who benefited by them as research fellows grew rapidly. When war broke out, Harvard deliberately set aside research fellowship funds to be used later; it was impossible to find enough properly trained young doctors to expend them at the time and it seemed only fair to hold them in reserve for the benefit of returning veterans who might use them to great advantage later. Thus, the large number of Harvard research fellows in 1946 and 1947 is, in a sense, an artefact. Yet the trend of the curve is unmistakable.

The number of applicants for the College's research fellowships, in contrast, has remained almost constant each year. The correct interpretation of what this signifies is problematical. Does it mean that those who nominate candidates for the Fellowships are extremely critical and, as a result, that the College selects from only the topmost level of all young doctors who think they wish to pursue a research career? Or does it mean that so many research fellowships are now available as to dilute the value of those offered by the College, making them more commonplace and of no great distinction?

The correct answer to these questions, clearly, at present, is uncertain. Yet one disconcerting fact has appeared from this study. Of 16 Research Fellows appointed by the College, only two have joined it and only one has become an Associate. The remaining 13 have appeared to show no interest whatsoever in the College or what it stands for. This record is all the more disconcerting because, under the old by-laws, nearly all of this group were eligible to become associates when they accepted the fellowship and by now six of them have been certified by the American Board of Internal Medicine so that election to the College should not be too difficult. On the whole, either indifference to the College or ignorance of its work must be the explanation. In future, the College should cultivate the loyalty and interest of its research fellows more actively than it has in the past.

The College, through its Research Fellowships, has conducted an interesting experiment in medical education which already has yielded interesting results. The continuance of the experiment for a longer period of time seems justified. The Fellows, however, must always be chosen with particular care, and especially so in times when fellowship funds are prevalent.

Those selected must appear to offer promise of achieving national prominence in medicine from the impetus they obtain at the beginning of their careers as Research Fellows of the American College of Physicians. If other than young people of rare ability and earnestness of purpose receive it, the Fellowship will degenerate and its maintenance will fail to promote and advance clinical research in any distinctive fashion of which the College can be proud.

REGINALD FITZ, M.D., F.A.C.P.*

* Chairman, Committee on Fellowships and Awards, 1947.

REVIEWS

Allergy in Theory and Practice. By ROBERT A. COOKE, M.D., ScD., F.A.C.P., Attending Physician and Director of the Department of Allergy, The Roosevelt Hospital, New York City, and Associates. 572 pages; 16 × 24 cm. 1947. W. B. Saunders Company, Philadelphia, Pennsylvania. Price, $8.00.

This volume represents a series of articles by Dr. Cooke and thirteen collaborators based upon the less formal lectures given in courses on allergy arranged in coöperation with the American College of Physicians. The magnitude of Dr. Cooke's contribution is evidenced by his being responsible for approximately 241 pages of the text.

The volume was designed to orient physicians to allergy rather than to offer an exhaustive text on the one hand or, to present the material in such simple language that the layman or the totally uninformed physician could understand the subject. The attitude of the authors is that a reasonable well educated physician can understand a technical subject if it is clearly presented without cheapening the presentation with futile attempts at over-simplification. This volume places allergy in the general field of medicine with gratifying precision. It shows its relationship to immunological processes and, also clinical medicine.

As his dominant rôle in this phase of the subject would suggest, Dr. Cooke's contribution on the basic processes is excellent, particularly as they concern immunologic mechanisms. The same is true of Heidelberger's section on the immuno-chemistry of antigens and antibodies.

The other portions of the book on the clinical phases of allergy are entirely adequate if the purpose of the book is kept in mind, namely, the introduction of allergy to physicians rather than a detailed text covering every aspect of the subject. It should be particularly valuable as a source of teaching material for undergraduate medical students.

The reviewer heartily recommends this book and is of the opinion that, in a distinguished fashion, it has accomplished the purpose for which it was designed.

H. M. B.

The Acute Infectious Fevers, An Introduction for Students and Practitioners. By ALEXANDER JOE, D.S.C., M.D.(Ed.), F.R.C.P.(Ed.), D.P.H., D.T.M. & H., Medical Superintendent, City Hospital, Edinburgh, Lecturer on Infectious Diseases to the University of Edinburgh, Formerly Medical Superintendent, North-Western Hospital, London. 276 pages, 13.5 × 22.5 cm. 1947. The Blakiston Co., Philadelphia, Pa. Price, $4.50.

The author has provided the answers to many practical questions confronting practitioners who treat the common acute infectious fevers. Logically presented are the pathology, etiology, transmission, infectivity, incubation and quarantine period, clinical features, complications, diagnoses, prognoses, prophylaxis and treatment of each individual entity. Of great value are the pertinent new researches, laboratory procedures and therapeutic weapons needed for the modern handling of infectious processes. Abundantly and well illustrated, clearly written, this book will serve the student and general practitioner. The sections on scarlet fever, diphtheria and cerebral spinal fever are outstanding, but the author's conception of all the fevers is thoroughly modern.

T. E. W.

Advances in Pediatrics (Volume II). Editorial Board: S. Z. LEVINE, Cornell University Medical College, New York; ALLAN M. BUTLER, Harvard Medical School,

Boston; L. Emmett Holt, Jr., New York University, College of Medicine, New York; A. Ashley Weech, Univ. of Cincinnati College of Med., Cincinnati. 409 pages; 24 × 16 cm. 1947. Interscience Publishers, Incorporated, New York. Price, $6.75.

After an absence of five years, the second volume of the series, "Advances in Pediatrics," makes its appearance and a welcome one it is.

The book follows closely the pattern set down by the editor of the initial volume. The book consists of an excellent collection of comprehensive personalized monographs by outstanding authorities on selected subjects of pediatric interest. The pediatric menu is as follows: etiology of congenital malformations, acute infectious lymphocytosis, rôle of fluorine in prevention and treatment of dental caries, the treatment of purulent meningitides, chemotherapy, atypical pneumonia, endocrine and other factors influencing the growth of children, virus diarrhea, prematurity, genesis of physiologic hyperbilirubinemia and prevention of recurrences of rheumatic fever. Each of the sections is accompanied by an extensive bibliography to recent literature.

The volume is larger by one hundred pages than its predecessor, contains eighty well selected illustrations and numerous tables.

Several chapters were of particular interest to this reviewer. The section on prematurity puts emphasis on the "physiologic handicaps" and metabolism of the premature infant. This is discussed in a concise, complete manner. The use of low fat feedings for prematures in the form of skimmed milk preparations is advocated, based on the author's original work in association with one of the editors (Gordon and Levine).

Stimulating reading is provided by the paper on etiology of congenital malformations, which directs attention toward the line of teratologic investigation.

The aims of the editors are well carried out in the volume. It is highly recommended to all students of pediatrics who desire to keep abreast of present developments.

A. H. F.

The X-Ray Treatment of Accessible Cancer. By W. Waldron Smithers, M.D., D.M.R. 147 pages; 19 × 27.5 cm. The Williams & Wilkins Co., Baltimore. 1946. Price, $8.50.

The book deals with cancer in accessible areas or in areas made accessible by surgery. The material is very well illustrated (many of the photographs being in color) and numerous tables summarize the results. The author stresses the importance of adapting the technic of treatment to the clinical condition met with, in order that radiation therapy may be placed on a more rational basis.

A method of gauging the response of the tumor to radiation is described. Serial biopsies are taken and in the sections "cells in the growing portions of the tumor are counted and classified into: (1) mitotic; (2) degenerating; (3) differentiating and (4) resting cells"—the proportions of each are then plotted in a graph against time. From this the radiologist can determine if treatment is sufficient, inadequate or ineffectual. If ineffectual, surgery can be resorted to before the disease has time to get out of control.

The author stresses the need for very complete records, as to full description of extent of the disease (including measurements of primary), details of treatment and adequate follow-up; for without them our own results cannot be evaluated nor can results of various clinics be compared with any degree of accuracy.

This book will prove of value as a reference to practicing radiologists and especially in those clinics which train men.

A. G. S.

BOOKS RECEIVED

Books received during September are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

American Illustrated Medical Dictionary (The) (21st Edition). By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S., Lt. Col., M.R.C., U. S. Army, Member of the Committee on Nomenclature and Classification of Diseases of the American Medical Association, etc. 1660 pages; 24 × 16 cm. 1947. W. B. Saunders Company, Philadelphia. Price, $8.00 without thumb index; $8.50 with thumb index.

Calcific Disease of the Aortic Valve. By HOWARD T. KARSNER, M.D., and SIMON KOLETSKY, M.D., Institute of Pathology, Western Reserve University and the University Hospitals of Cleveland. 111 pages; 23.5 × 15.5 cm. 1947. J. B. Lippincott Company, Philadelphia. Price, $5.00.

Developmental Diagnosis: Normal and Abnormal Child Development—Clinical Methods and Pediatric Applications (2nd Edition, Revised and Enlarged). By ARNOLD GESELL, M.D., and CATHERINE S. AMATRUDA, M.D. 496 pages; 24 × 16 cm. 1947. Paul B. Hoeber, Incorporated, Medical Book Department of Harper & Brothers, New York. Price, $7.50.

Dictionary of the Physiology of Man (in Italian). By GAETANO MARTINO, Professor of Human Physiology at the University of Messina, Sicily. 305 pages; 24.5 × 18 cm. 1945. Azienda Poligrafica Editoriale, Catania, Italy. Price, 800 lire.

Erkrankungen des Uropoetischen Systems und der Prostata durch Storung der Blutstromung (in German). By PROFESSOR KARL HUTTER, Facharzt for Urologie, Wiener Beitrage zur Urologie, Herausgegeben von Prof. Dr. Richard Ubelhor: Band I. 200 pages; 23.5 × 16 cm. 1947. Grune & Stratton, Inc., New York. Price, $4.00.

Internal Medicine in General Practice (2nd Edition). By ROBERT PRATT MCCOMBS, B.S., M.D., F.A.C.P., Assistant Professor of Medicine and Director of Postgraduate Teaching, Tufts College Medical School, etc. 741 pages; 24.5 × 16.5 cm. 1947. W. B. Saunders Company, Philadelphia. Price, $8.00.

An Introduction to Biochemistry (3d Edition). By WILLIAM ROBERT FEARON, M.A., Sc.D., M.B., Fellow of Trinity College and Professor of Biochemistry, University of Dublin, etc. 569 pages; 22.5 × 14.5 cm. 1947. Grune & Stratton, Inc., New York. Price, $6.00.

Lessons of Medical Clinic, Vol. I (in Italian). By LUIGI CONDORELLI, University of Catania. 187 pages; 21 × 15 cm. 1947. Azienda Poligrafica Editoriale, Catania. Price, 655 lire.

Morphologic Hematology, Special Issue No. 1 of BLOOD, The Journal of Hematology. By WILLIAM DAMESHEK, M.D., Editor-in-Chief. 200 pages; 26 × 18 cm. 1947. Grune & Stratton, Inc., New York. Price, $4.75.

Ocular Therapeutics. By WILLIAM J. HARRISON, Phar.D., M.D., F.A.C.S., Associate Professor in Ophthalmology, Jefferson Medical College, etc. 112 pages; 20 × 14.5 cm. 1947. Charles C. Thomas, Springfield, Illinois. Price, $3.50.

Pharmacology, Therapeutics and Prescription Writing: For Students and Practitioners (5th Edition). By WALTER ARTHUR BASTEDO, Ph.G., Ph.M/. (Hon.), M.D., ScD. (Hon.), F.A.C.P., Consulting Physician, St. Luke's Hospital, New York, etc. 840 pages; 24.5 × 16.5 cm. 1947. W. B. Saunders Company, Philadelphia. Price, $8.50.

Physiopathology of the Veinous Circulation (in. Italian). By LUIGI CONDORELLI, Director of Medical Clinic at the University of Catania, Sicily. 336 pages; 25 × 17.5 cm. 1947. A.P.E. Degli; U. & G. Pagnano, Catania. Price, 1200 lire. (Publishers have provided for translation into English.)

Rypin's Medical Licensure Examinations: Topical Summaries, Questions, and Answers (6th Edition). Under the Editorial Direction of WALTER L. BIERRING, M.D., F.A.C.P., M.R.C.P., Edin. (Hon.), Former Member, National Board of Medical Examiners, etc. 690 pages; 24 × 16 cm. 1947. J. B. Lippincott Company, Philadelphia. Price, $6.00.

A Textbook of Clinical Neurology, With an Introduction to the History of Neurology (6th Edition). By ISRAEL S. WECHSLER, M.D., Clinical Professor of Neurology, Columbia University, New York, etc. 829 pages; 24.5 × 16.5 cm. 1947. W. B. Saunders Company, Philadelphia. Price, $8.50.

Time for Circle and Districtal Speed of Current in Physiopathology and in Clinic (in Italian). By A. FRANCAVIGLIA and A. TURCHETTI, with a preface by PROF. L. CONDORELLI. 254 pages; 24.5 × 17 cm. 1946. Azionda Poligrafica Editoriale, Catania. Price, 680 lire.

Trichomonas Vaginalis and Trichomoniasis. By RAY E. TRUSSELL, M.D., Associate in Hygiene and Preventive Medicine, etc. With an Introduction by E. D. PLASS, M.D., Professor of Obstetrics and Gynecology, State University of Iowa. 277 pages; 23.5 × 15.5 cm. 1947. Charles C. Thomas, Springfield, Illinois. Price, $6.00.

COLLEGE NEWS NOTES

American Board of Internal Medicine

Memorandum to Applicants for Admission to Examination

(Revised July 1947)

Organization

The American Board of Internal Medicine was established in 1936 by joint action of the Section on the Practice of Medicine of the American Medical Association and the Board of Regents of the American College of Physicians. It is a non-profit organization incorporated for the benefit of physicians who, because of their training and experience, desire to be certified formally as specialists in Internal Medicine by a representative group of their colleagues.

The Board consists of twelve members; seven are nominated by the American College of Physicians and five by the Section on Internal Medicine (formerly the Practice of Medicine) of the American Medical Association. Each member of the Board serves for a term of three years but may be nominated and elected for a second term of three years. However, no member may serve for longer than two successive terms. The service is voluntary and members of the Board do not receive compensation beyond the actual expenses incurred at the oral examinations or at special meetings.

Responsibilities of the Board

The major object of the Board is to pass judgment on the competence of internists who desire certification—not to determine who shall or shall not practice internal medicine as a specialty.

The American Board of Internal Medicine is not concerned with any mechanism which gains special privileges or specific recognition for those physicians who have been certified in internal medicine. It has never been the intent of the Board to define requirements for membership on the staffs of hospitals.

This Board endorses completely the stand of the American Board of Surgery which "specifically disclaims interest in or recognition of differential emoluments that may be based on certification."

Requirements for Admission to Examination and Certification

Each applicant for certification by this Board must satisfy the qualifications listed below. (I) General Qualifications A, B, C. D. (II) Professional Qualifications A, B, C, D. For exceptions to the requirements C and D under Professional Qualifications, see Page 848, Paragraph G.

I. *General Qualifications*

A. All candidates must be citizens of the United States or Canada.

B. All candidates must present evidence of satisfactory moral and ethical standing in the medical profession.

C. All candidates must be active members in good standing in their County and State medical societies in their state of legal residence.

(This ruling shall not apply to commissioned officers of the United States regular Army or Navy while serving outside the territorial limits of the United States.)

D. Canadian citizens applying for admission to examination must be active members of the Canadian Medical Association.

II. *Professional Qualifications*

A. Graduation from a medical school approved by the Council on Medical Education and Hospitals of the American Medical Association at the date of graduation.

B. Satisfactory completion of an approved interneship of not less than twelve months.*

C. Approved residency or fellowship training in internal medicine according to the following plan (Plan A) or one of the alternate plans described under paragraph D.

Plan A. A residency or fellowship in internal medicine for a period of not less than three years in a hospital or other institution approved by the Council on Medical Education and Hospitals of the American Medical Association for residency or fellowship in internal medicine. In addition, two years of practice of clinical internal medicine will be required. The Board will accept the following equivalents as satisfying one year only, of the three years of residency or fellowship to which this paragraph refers.

1. A second year (or a part thereof) of approved interneship in a hospital approved for resident training in internal medicine if limited to the medical service (or medical specialties noted under 2) for one year and if recognized as being the equivalent of an assistant residency by the Medical Director of the hospital and the Chief of the Medical Service.

2. One year of approved residency in one of the medical specialties: Allergy, Cardiovascular Disease, Gastro-Enterology, Hematology, Pulmonary Diseases, Neurology, Pediatrics, and Psychiatry.

3. One year of approved residency in Pathology.

4. One year as a graduate student or as an instructor in an approved medical school on a full time basis in Bacteriology, Biochemistry, Pathology, Pharmacology, Physiology, or Internal Medicine.

5. An advanced degree in the fundamental sciences.

Note: Graduate training credit for the time involved will be allowed veterans and other candidates who take and satisfactorily complete post-graduate courses in internal medicine or the basic medical sciences provided by accredited medical schools. This ruling shall not apply to courses of less than three months' or more than twelve months' duration. A certificate of creditable performance, based in part, at least, on a formal examination upon completion of the course, will be required.

D. Alternate Training Plans: The Board firmly believes that the plan of intensive training prescribed above offers the best opportunity for a young physician to prepare himself to meet his responsibilities as a specialist in internal medicine. It is recognized, however, that capable individuals may accomplish the same result in a longer period of time during which the training is less intensive. The Board realizes that a number of medical graduates cannot follow the shorter and more desirable plan either because suitable residencies are not available, or in some instances because of personal and economic reasons. Accordingly the Board has modified its previous regulations governing eligibility for admission to examination. In doing so the Board has not modified its standards of examination. It has liberalized its eligibility requirements for admission to examination by accepting half-time formal training, and the practice

* During the period in which the 9–9–9 program was in effect an approved interneship of nine months will satisfy the requirement of twelve months. A residency of nine months is considered as nine months only.

of internal medicine under favorable circumstances as to professional and hospital contacts, in lieu of part of the full-time requirements. It is hoped that by this means exceptional individuals may acquire a knowledge of medicine and experience in its application sufficient to qualify for certification.

The program already described (Plan A), which consists of three years of formal training in an approved residency or its equivalent, following interneship, and two additional years in the practice of internal medicine, is recommended by the Board. Variations in this program are now made subject to the following regulations. (See illustrated plans.)

1. In all instances, one year of approved interneship and one year of approved residency will be required, except as indicated under Plan "G." The graduate training credit of one year heretofore granted as a result of active duty as a commissioned officer in the Armed Forces during the period beginning December 7, 1941, and ending January 1, 1947 may not be applied in satisfaction of the one year of approved residency referred to in Plans D, E, F, unless the candidate's assignment is considered by the Board to have been equivalent to an approved residency.

2. Following one year of interneship and two years of approved residency,* the remaining requirements may be satisfied by:

(*Plan B*) That is, by two years of half-time formal training followed by two years of practice limited to internal medicine, or by
(*Plan C*) That is, by five years of practice limited to internal medicine.

3. Following one year of interneship and one year of approved residency, the remaining requirements may be satisfied by:

(*Plan D*) That is, by four years of half-time formal training followed by two years of practice limited to internal medicine, or by,
(*Plan E*) That is, by two years of half-time formal training followed by five years of practice limited to internal medicine, or by,
(*Plan F*) That is, by eight years of practice limited to internal medicine.

4. In every instance at least two years of practice in internal medicine must be included, but in instances in which four years of practice are substituted for one year of residency, only one additional year of practice will be required; when more than eight years of practice are substituted for two years of residency an additional year of practice will not be required.

5. Physicians who have practiced internal medicine for twelve years following an approved interneship may qualify for the examinations without further training (*Plan G*).

Half-time formal training under expanded Plans B, D, and E is defined as follows:

1. Half-time † as an instructor in clinical medicine in a recognized medical school in the United States or Canada.
2. Half-time † in a research fellowship sponsored by a recognized medical school in the United States or Canada.
3. Half-time † as a graduate student in an approved graduate medical school in the United States or Canada.

E. Practice Requirements: A period of not less than two years of practice in the general field of clinical internal medicine or in the more specialized branches of medicine. (See exceptions—Par. 9, Page 846.) This requirement may be satisfied by independent practice or in association with a recognized internist.

* For the second year of approved residency one of the equivalents described under C may be substituted.

† Certification by the head of department in which the work was done is required.

Note: Although in general the Board believes it desirable to complete the three years of formal training before satisfying the requirements of practice a reversal of this order is acceptable.

F. Graduates of Foreign Schools: At the present time neither the Council on Medical Education of the American Medical Association nor any other educational agency in the United States has the machinery to evaluate adequately the quality of foreign medical education. This Board must, therefore, evaluate the fundamental educational credentials and other qualifications of each individual candidate educated abroad who applies for admission to examination. (Requirements for graduates of foreign schools may be obtained on request to the Board—One West Main Street, Madison 3, Wisconsin.)

G. Candidates Graduating Prior to 1937: The requirement of three years of graduate training will not apply to candidates graduating from approved medical schools in the United States and Canada in 1936 or previous thereto, provided such candidates have limited their work to the field of internal medicine for at least two years, and provided each candidate is recognized as an internist by his colleagues in his community.

H. "Preceptor Training": Preceptor type training is not recognized in satisfaction of any part of the three year requirement of formal graduate training.

I. The Board will grant one year of graduate training credit, or one year in satisfaction of the requirements of practice, regardless of assignment, for active duty as a commissioned officer in the United States Army, Navy, or United States Public Health Service for one year or more, beginning on or subsequent to December 7, 1941 and terminating on or before January 1, 1947.

Depending upon the nature of the duty assignments, after January 1, 1947 active duty as a commissioned officer in the United States Army Reserve Corps, United States Naval Reserve Corps, or United States Public Health Service may be applied in satisfaction of one year of the requirements of practice but will not be regarded as satisfying any part of the graduate training requirements, unless the officer is assigned as a resident in Internal Medicine, Neurology, Psychiatry, or Pathology in an Army, Navy or United States Marine Hospital which is approved by the Council on Medical Education and Hospitals of the American Medical Association for resident training in the divisions of medicine referred to.

Principles of Training

The American Board of Internal Medicine is interested in the fact that the candidate has embarked on a career of study voluntarily and has thereby expressed the desire to excel and to participate personally in the world's progress in Medicine.

Preparation must be based on years of continuous thoughtful study. Therefore, in suggesting a program for those who wish advice, the Board hopes to assist the candidates to avoid inferior and superficial programs which may lead to failure and disappointment in later years.

The Board believes that all internists should have a sound fundamental knowledge of Anatomy, Bacteriology, Biochemistry, Pathology, Pharmacology, and Physiology. Such knowledge is essential to the continued progress of any internist. The Board anticipates that adequate training will be obtained in the basic sciences as applied to internal medicine during a formal three year residency program.

The Board wishes to emphasize that time and training are but a means to the end of acquiring a broad knowledge of internal medicine which the candidate must demonstrate to the Board in order to justify it in certifying that he is competent to practice internal medicine as a specialty. The responsibility of acquiring the knowledge rests with the candidate. The responsibility of maintaining the standards of knowledge required for certification devolves on the Board.

Application

Candidates for examination must make their application on a prescribed form which may be obtained from the office of the Assistant Secretary-Treasurer.

The application must contain a record of the candidate's premedical and medical training as well as of interneships, residencies, graduate study, hospital or dispensary staff appointments, teaching positions, service in the armed forces, membership in medical societies, medical papers published, and the names of three or more well known internists to whom the Board may write for professional and character reference.

The application must be accompanied by one recent, signed photograph of the candidate mounted on the application, and the registration and examination fee of thirty dollars, which fee will cover both the written and oral examinations. An additional fee of ten dollars will be required when the certificate is issued.

Method of Examination

The examinations for certification by the Board comprise two parts: Part I is written; Part II is clinical and is an oral examination. The written examination is held simultaneously in different sections of the United States and Canada on the third Monday of February and October of each year. This examination is divided into a morning and afternoon period for each of which three hours are allowed. The questions asked are framed in such manner as the Board elects; in general, there will be questions designed to test the applicant's knowledge of applied physiology, anatomy, physiological chemistry, pathology, bacteriology, and pharmacology as related to internal medicine, and his basic clinical acumen.

Candidates must pass the written examination before admission to the oral examination will be authorized. The oral examination is conducted under the direct supervision of the Board. It is held near the time and place of the annual meetings of the American Medical Association and the American College of Physicians. The examination is conducted at the bedside of the patient. Each candidate is assigned two or more patients and is expected to be sufficiently familiar with whatever problems present themselves to satisfy the Board of his clinical expertness.

Reëxamination

Effective January 1, 1946, not more than three written examinations will be authorized. The interval between the first and the second written examinations will be one year. The interval between the second and third written examinations will be not less than two years. A longer period may be required by the Board. A fee of ten dollars is required for each additional written examination.

This ruling does not make it mandatory for a candidate to repeat the examination within one or two years, since each candidate may elect a longer interval.

Not more than three oral examinations are authorized. The interval between the first and second oral examinations will be one year. The interval between the second and third oral examinations will be not less than two years. A longer period may be required by the Board. Candidates may elect a longer interval if desired. A fee of ten dollars is required for each additional oral examination.

Certificates

The certificate issued by the American Board of Internal Medicine shall be in such form as to comply with the articles of incorporation and the bylaws and shall be signed by the officers and members of the Board and shall bear the official seal of the Board.

Certificates of the Board will be issued to candidates who have satisfactorily completed the written and oral examinations and have been found qualified by the Board to practice the specialty of internal medicine. Specialty certification will be designated on the certificate, for those so certified.

Advisory Boards

Allergy, Cardiovascular Disease, Gastroenterology, and Pulmonary Diseases are recognized specialties.

All candidates must pass the written and oral examinations in internal medicine before admission to examination in a specialty of medicine. The specialty examinations are oral only and may be taken the day following the examination in general medicine, or at any other regularly scheduled oral examination.

Applications for consideration in the specialties referred to must be approved by the Advisory Board concerned and confirmed by this Board.

Application forms will be forwarded upon request to the office of the Assistant Secretary-Treasurer, William A. Werrell, M.D., One West Main Street, Madison 3, Wisconsin.

An orientation course in clinical allergy, to be given by the American Academy of Allergy, under the sponsorship of the University of Michigan Department of Postgraduate Medicine, is a five day course designed to cover the new and pertinent facts of clinical allergy. The faculty will consist of nationally and inter-nationally known men in the field of allergy, and members of the faculty of the University of Michigan Medical School who are qualified to discuss the inter-relationship of allergy to other fields of medicine. Lectures and case demonstrations will be used to illustrate the problems of diagnosis, and modern management of bronchial asthma, seasonal hay fever, allergic rhinitis, atopic eczema, juvenile eczema, migrainous headaches, gastrointestinal allergy, allergic eye disease, contact and occupational dermatitis, allergic blood dyscrasia, and drug allergy. Fee, $40.00. Registrants: Minimum, 30; maximum, 60. December 8 to 12. Request for further information should be addressed to: Howard H. Cummings, M.D., Department of Postgraduate Medicine, University Hospital, Ann Arbor, Michigan.

A course in Electrocardiographic Interpretation for *graduate physicians* will be given at the Michael Reese Hospital Postgraduate School by Dr. Louis N. Katz, Director of Cardiovascular Research. The class will meet each Tuesday from 7:00 to 9:00 p.m. for twelve weeks, beginning February 7, 1948.

Further information and a copy of the lecture schedule may be obtained upon application to the Office of the Dean, Michael Reese Hospital Postgraduate School, Chicago 16, Illinois.

ADDITIONAL LIFE MEMBERS

The College takes pleasure in announcing that, on October 11, 1947, the following Fellows became Life Members of the College:

Edgar R. Miller, M.D., F.A.C.P., Wilmington, Del.
Tom B. Throckmorton, M.D., F.A.C.P., Des Moines, Iowa

The Association of American Physicians will hold its Annual Meeting in Haddon Hall, Atlantic City, N. J., on May 4–5, 1948. The Society for Clinical Investigation will hold its meeting at the same hotel on May 3.

The American College of Radiology will hold its 1948 Annual Meeting on July 20, 1948, at the Sheraton Hotel in Chicago.

The Colorado State Medical Society will have its 1948 Annual Session September 22–25 at Glenwood Springs, Colorado.

The Annual Convention of the American Academy of Allergy will take place December 15–17, 1947, at St. Louis, Mo., in the Hotel Jefferson.

U. S. Public Health Service Research Fellowships

The U. S. Public Health Service will award Research Fellowships for the training and development of medical scientists. A "Pre-doctorate" fellowship is offered with a stipend ranging from $1200 to $1600 and tuition a year to holders of the Bachelor's degree who have completed a year or two of their medical course and who desire to devote several years to the study of a basic science before completing their medical studies. A similar fellowship with stipend ranging from $1600 to $2000 and tuition is offered for those who have a Master's degree. "Post doctorate" fellowships are available to physicians or holders of the M.D. degree, or Ph.D. degree in a medical science. While tuition costs are not defrayed in these cases, stipends from $3000 to $3600, with an increase of $300 each year, are given. For applicants who meet the requirements for the latter fellowships, and who have special ability or training, there are available "Special research" fellowships. In these cases, the stipend is adjusted to the need. Applications for these fellowships may be secured from the Division of Research Grants and Fellowships of the National Institute of Health, Bethesda 14, Md.

The State Health Department's Cancer Division of Pennsylvania has allocated $30,000 to the University of Pennsylvania School of Medicine and Hospital, for the purpose of giving postgraduate courses in the diagnosis and treatment of cancer. The University will give three courses of two weeks each during the 1947–1948 school year on the theory, pathology, diagnosis, and treatment of cancer.

The Medical Society of Virginia on October 13–15, 1947, at its Annual Meeting at Roanoke, celebrated its 100th Meeting. However, the Society was first organized in the latter part of 1820, and there were some intermissions through the several wars.

Dr. Wyndhand Blanton, F.A.C.P., of Richmond, one of the foremost historians of the Society, gave an address on "1820—The Virginia Doctor and His Times."

The Twenty-fifth Annual Fall Clinical Conference of the Kansas City Southwest Clinical Society was held at Kansas City, October 6–9, inclusive, 1947. Among the guest speakers were the following: Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio, "Congenital Hemolytic Jaundice," "Gout," and "Precipitating and Accelerating Factors in Arthritis"; Dr. Willard O. Thompson, F.A.C.P., Chicago, Ill., "Uses and Misuses of the Sex Hormones," "Endocrine Problems in Adolescence," and "The Management of Obesity"; Dr. Leon Schiff, F.A.C.P., Cincinnati, Ohio, "Hematemesis and Melena," "The Differential Diagnosis of Jaundice," and "The Diagnosis

of Gastric Cancer"; Dr. Eugene P. Pendergrass, F.A.C.P., Philadelphia, "How to Prevent Death from Breast Cancer," "Experiences at Bikini," and "Treatment of Deafness in Children by Radium"; Dr. William D. Stroud, F.A.C.P., Philadelphia, Pa., "Coronary Artery Disease," "Hypertension," and "The Treatment of Congestive Heart Failure"; Dr. Joseph S. D'Antoni, F.A.C.P., New Orleans, La., "Amebiasis," and "The Chronic Diarrheas."

The Chicago Medical Society has initiated a series of short-term postgraduate medical courses this Autumn by offering a course in cardiovascular diseases, October 2–25, and one in gastro-enterology, October 27 to November 1. The courses were planned by the Society's Committee on Postgraduate Medical Education, of which Dr. Willard O. Thompson, F.A.C.P., is Chairman, and Drs. A. C. Ivy, F.A.C.P., J. Roscoe Miller, F.A.C.P., and John B. Youmans, F.A.C.P., are members. The courses have been organized much along the lines of those pioneered by the College, and the instructional officers include many Fellows of the College from the Chicago area as well as from more distant cities. Designed for specialists and general practitioners alike, the courses were approved for the training of veterans.

In recognition of the growing importance of alcoholism as a social problem in California, a second Institute on Alcoholic Studies was presented during October at the Los Angeles campus of the University of California. A three-day program, in which social, political, religious, and scientific leaders from California and from the Yale School of Alcohol and Studies participated, covered the following topics: The Problem of Alcoholism in California; Individual and Social Aspects of Alcoholism; Alcoholism as an Individual Problem; Alcoholism as a Public Problem. Among the speakers was Dr. Lawrence Kolb, F.A.C.P., Sacramento, Medical Deputy Director of the Department of Mental Hygiene.

North Dakota Regional Meeting

The first Regional Meeting of the American College of Physicians for the State of North Dakota was held at Bismarck, September 13, 1947, under the Governorship of Dr. Robert B. Radl. All but four members from North Dakota were in attendance, and there were a goodly number of guests. An excellent all-day scientific session was held, with an informal reception and dinner in the evening. All present expressed the desire to have the meeting repeated as a yearly occurrence.

Iowa Regional Meeting

The first Regional Meeting of the American College of Physicians for the State of Iowa was held at Des Moines on September 27, 1947, under the Governorship of Dr. B. F. Wolverton, F.A.C.P., of Cedar Rapids, and the local Chairmanship of Dr. Maurice J. Rotkow, F.A.C.P., of Des Moines. Thirty-six College members and twelve guests were in attendance. The total College membership of Fellows and Associates for Iowa is fifty-five. Thus two-thirds of the members of the state were in attendance. Dr. Albert M. Snell, F.A.C.P., of the Mayo Clinic at Rochester, Minnesota, was the guest speaker, his subject being "Clinical and Psychological Consideration of Patients with Cirrhosis." At the evening session, Dr. Walter L. Bierring, F.A.C.P., of Des Moines, former Regent of the College, spoke on "The American College of Physicians in Retrospect and in Prospect."

Programs of Recent Regional Meetings

The programs of the following recent Regional Meetings of the College are taken, in condensed form, from the printed programs distributed to members of the College in the respective areas. Information concerning registration or special events at these meetings was not available at the time this material went to the press.

Western New York

This meeting took place at Syracuse on Tuesday, October 28, under the Governorship of Edward C. Reifenstein, M.D., F.A.C.P. Speakers were drawn from various cities in the newly enlarged Western New York territory. The morning program included papers by the following: Herbert R. Brown, Jr., M.D. (by invitation), Rochester, The Ballistocardiogram and Its Use in Cardiology—Discussion and Motion Pictures; Allan D. Bass, M.D. (Associate), Syracuse, The Use of Mustard Gas in the Treatment of Blood Dyscrasias; Simon Propp, M.D. (by invitation), Albany, Recent Studies of Multiple Myeloma—Results of Treatment with Stilbamidine; George H. Reifenstein, M.D. (Associate), Syracuse, Electrocardiographic Heart Disease; Eugene L. Lozner, M.D. (Associate), Syracuse, The Pathologic Physiology of Hemorrhagic Diathesis; Charles G. Craddock, Jr., M.D. (by invitation), Rochester, Hemophilia—The Report of the Mechanism of the Development and Action of an Anticoagulant in Two Cases; Roger S. Mitchell, Jr., M.D., F.A.C.P., Trudeau, The Value of Pneumoperitoneum in the Treatment of Pulmonary Tuberculosis. The meeting then recessed from the Syracuse University College of Medicine to the Onondaga Golf and Country Club for the remainder of the program. The afternoon session included talks on the following subjects: Pulmonary Ventilation—Its Determination by Four Simple Clinical Methods, by James Monroe, M.D. (Associate), Ray Brook; The Management of Hypertension, Richard H. Lyons, M.D., F.A.C.P., Syracuse; Streptomycin in Pulmonary Tuberculosis—A Preliminary Report, John N. Hayes, M.D., F.A.C.P., Saranac Lake; The Toxic Effect of Streptomycin, Paul Bunn, M.D. (by invitation), Syracuse; Physiological Changes Associated with the Ill Effects of Heat, John H. Talbot, M.D., D.Sc. (by invitation) Buffalo. A clinicopathological conference was led by J. Howard Ferguson, M.D. (by invitation), Syracuse, with discussion by George M. Mackenzie, M.D., F.A.C.P., Albany, and Ronald L. Hamilton, M.D., F.A.C.P., Binghamton. A reception and cocktails were followed by dinner at the Club. The guest speakers listed were Hugh J. Morgan, M.D., F.A.C.P., Nashville, Tenn., President of the College; Asa L. Lincoln, M.D., F.A.C.P., New York, Governor for Eastern New York; Herman G. Weiskotten, M.D., Dean, College of Medicine, Syracuse University; Albert C. Bickelhaup, D.D.S., Syracuse; and E. R. Loveland, Philadelphia, Executive Secretary of the College.

New Jersey

The first New Jersey Regional Meeting of the College was held at the Downtown Club, Newark, on Friday, November 7, under the Governorship of George H. Lathrope, M.D., F.A.C.P. Andrew J. V. Klein, M.D., F.A.C.P., Newark, served as chairman of arrangements. Lewis Barr Flinn, M.D., F.A.C.P., Wilmington, Del., and Asa L. Lincoln, M.D., F.A.C.P., New York, N.Y., College Governors for Delaware and Eastern New York, respectively, presided at the afternoon scientific session. Papers in this program were as follows: Spinal Cord Changes in Pernicious Anemia, with Suggestive Treatment, by Clarence L. Andrews, M.D., F.A.C.P., Atlantic City; Early Detection of Cancer, John E. Leach, M.D., F.A.C.P., Paterson; Probacil Therapy, Walter A. Crist, M.D. (Associate), Camden; Rectosigmoidal Lesions, Johannes F. Pessel, M.D., F.A.C.P., Trenton; Meigs' Syndrome, Abraham E. Jaffin,

M.D., F.A.C.P., Jersey City; Management of the Rheumatic Patient, Jerome G. Kaufman, M.D., F.A.C.P., Newark; Use of Estrogens in Internal Medicine, Elmer L. Sevringhaus, M.D., F.A.C.P., Nutley. Cocktails and a dinner, at which Dr. Lathrope was toastmaster, followed; the guest speaker was George Morris Piersol, M.D., M.A.C.P., Philadelphia, Secretary-General of the College.

Kentucky

The first post-war Kentucky Regional Meeting of the College, under the Governorship of Chauncey W. Dowden, M.D., F.A.C.P., took place at Louisville on Saturday, November 8. General chairman of the meeting was G. W. Pedigo, Jr., M.D., F.A.C.P. In addition to a panel discussion of The Place of Vagotomy in the Treatment of Peptic Ulcer, in which Drs. Samuel A. Overstreet, F.A.C.P., R. Arnold Griswold, F.A.C.S. (by invitation), John D. Trawick, Jr. (Associate), and Hampden C. Lawson (by invitation), participated, the afternoon session at the Louisville General Hospital offered the following papers: Needle Biopsy of the Liver as a Diagnostic Aid in Hepatic Disease, by Herbert M. Clay, M.D. (by invitation); Recent Advances in the Treatment of Blood Dyscrasias and Allied Conditions, Marion F. Beard, M.D., F.A.C.P.; Modern Concepts in the Diagnosis and Treatment of Congenital Heart Disease, Ralph Adams, M.D., F.A.C.S.; all of the foregoing authors from Louisville; Cytological Study of the Sputum in the Diagnosis of Pulmonary Malignancy, Thornton Scott, M.D., F.A.C.P., Lexington. Guest speakers at the banquet at the Pendennis Club were Hugh J. Morgan, M.D., F.A.C.P., Nashville, Tenn., and E. R. Loveland, Philadelphia, Pa., President and Executive Secretary of the College, respectively.

Illinois, Indiana, Michigan, Minnesota, and Wisconsin

The Midwest Regional Meeting of the College occurred on Saturday, November 15, at the Schroeder Hotel, Milwaukee, Wis., with Karver L. Puestow, M.D., F.A.C.P., Governor for that State, as General Chairman, and Francis D. Murphy, M.D., F.A.C.P., as local Chairman of Arrangements. The meeting formed a part of Postgraduate Course No. 8, Internal Medicine, offered under the direction of William S. Middleton, M.D., F.A.C.P., Madison, Wis. The following papers were presented at the first part of the morning session, over which Douglas Donald, M.D., F.A.C.P., Detroit, Governor for Michigan, presided: Liver Biopsy Studies from Peritoneoscopy Specimens, by Merlyn C. F. Lindert, M.D. (Associate), Milwaukee; The Liver in Chronic Ulcerative Colitis, H. Marvin Pollard, M.D., F.A.C.P., Ann Arbor; Cystic Disease of the Liver, George F. O'Brien, M.D., F.A.C.P., Chicago; Results of Lipotropic Therapy in Cirrhosis of the Liver, Frederick Steigmann, M.D., F.A.C.P., Chicago; Recent Studies of Experimental Myocarditis, Franklin A. Kyser, M.D., F.A.C.P., Chicago; End Results in 33 Successfully Treated Cases of Subacute Bacterial Endocarditis with Particular Reference to the Clinical Evidence of Cardiac Efficiency, Walter S. Priest, M.D., F.A.C.P., Chicago; Endocarditis in the Elderly, Eugene F. Traut, M.D., F.A.C.P., Stanley Gumbiner, M.D. (by invitation), Raymond Hench, M.D. (by invitation), and J. Bailey Carter, M.D., F.A.C.P., all of Chicago; The Diagnostic Use of Radioactive Tracers, Kenneth Corrigan, Ph.D. (by invitation), Detroit.

Robert M. Moore, M.D., F.A.C.P., Indianapolis, College Governor for Indiana, presided at the second part of the morning session during which the following offerings were heard: Present Status of Antithyroid Drugs, William H. Beierwaltes, M.D. (by invitation), Ann Arbor; Present Status of Treatment of Toxic Goiter, Willard O. Thompson, M.D., F.A.C.P., Chicago; Gastric Polypi, James B. Carey, M.D., F.A.C.P., Minneapolis; Effect of Enterogastrone on Gastric Secretion in Man, Joseph

B. Kirsner, M.D. (Associate), and Erwin Levin, M.D. (by invitation), Chicago; Prognosis in Recent Myocardial Infarction, Louis N. Katz, M.D., F.A.C.P., Chicago; Enzyme Studies in the Cancer Problem, Van R. Potter, Ph.D. (by invitation), Madison; Studies on the Effect of Estrogens and Androgens on Mammary Cancer, Samuel G. Taylor, III, M.D., F.A.C.P., Danely P. Slaughter, M.D. (by invitation) and Edson Fairbrother Fowler, M.D. (by invitation), Chicago; Follicular Lymphoblastoma, Ovid O. Meyer, M.D., F.A.C.P., Madison.

Presiding officers at the afternoon session were Edgar V. Allen, M.D., F.A.C.P., Rochester, and Cecil M. Jack, M.D., F.A.C.P., Decatur, A.C.P. Governors for Minnesota and Southern Illinois, respectively. The afternoon program consisted of the following presentations: Diagnostic Problems with Fungus Infections of the Lungs, Edwin F. Hirsch, M.D., F.A.C.P.; Treatment of Bronchial Asthma, Leon Unger, M.D., F.A.C.P.; Duration of the Infection Following the Onset of Scarlet Fever, Paul S. Rhoads, M.D., F.A.C.P.; The Value of Vaccination against Epidemic Influenza in the Light of Recent Experience, Clayton Loosli, M.D. (by invitation); Clinical Evaluation of Several Medical Procedures Used in the Treatment of Common Peripheral-vascular Disorders, David I. Abramson, M.D., F.A.C.P.; Some New Theoretical Considerations of Blood Flow, Henry R. Jacobs, M.D., F.A.C.P.; Evaluation of the Present Forms of Treatment of Polycythemia Rubra Vera, Leon O. Jacobson, M.D. (Associate); Protective Action of Penicillin against Bacterial Endotoxins, Walter D. Hawk, M.D. (by invitation), Alden K. Boor, Ph.D. (by invitation), and C. Phillip Miller, M.D., F.A.C.P.; The Development of Bacterial Resistance to Streptomycin, by Dr. Miller; all of the foregoing speakers being from Chicago; Periarteritis Nodosa, Frederick W. Madison, M.D., F.A.C.P., Milwaukee; Classification of Congenital Hypothrombinemia, Armand Quick, M.D. (by invitation), Milwaukee; The Newer Anti-histamine Drugs, Sidney Friedlaender, M.D. (by invitation), Detroit.

The evening program included a reception, and a dinner at which LeRoy H. Sloan, M.D., F.A.C.P., Chicago, Regent of the College, was toastmaster. The list of distinguished guests included Ernest E. Irons, M.D., F.A.C.P., Regent and past President, Chicago; Walter L. Palmer, M.D., F.A.C.P., Chairman of the Board of Governors, Chicago; William S. Middleton, M.D., F.A.C.P., Madison, Regent; and Drs. Robert B. Radl, F.A.C.P., Bismarck, John L. Calene, F.A.C.P., Aberdeen, Joseph D. McCarthy, F.A.C.P., Omaha, Ernest D. Hitchcock, F.A.C.P., Great Falls, Benjamin F. Wolverton, F.A.C.P., Cedar Rapids, and Chauncey W. Dowden, F.A.C.P., A.C.P. Governors for North Dakota, South Dakota, Nebraska, Montana and Wyoming, Iowa, and Kentucky, respectively.

Questionnaires Returned Concerning San Francisco Annual Session

1361 members of the College have returned the questionnaires distributed in late August asking information about the attendance, program and other items concerning the Annual Session of the College at San Francisco, April 19–23, 1948. The returns indicate that there will be a very representative group from all parts of the United States and Canada in attendance at the meeting. While the majority will travel by railroad, there are some 300 who will go by air, and 200 who will go by automobile. Slightly over 80 per cent of the attendants will be accompanied by their wives or by guest physicians. Fully 600 are interested in a special train or trains which are in the course of arranging by the College. Announcements will follow later. It is now anticipated that a special train will operate from New York City, serving New England, the Middle Atlantic States; another special train from Chicago, accommodating those who will use that gateway; still a third special train is contemplated from the Southeastern, South Central and Midwestern States.

More than 100 are interested in a conducted tour to Hawaii. About three-quarters of this group are interested in making the trip both ways by ship, one-third wish to make the round trip by plane, and the balance are interested in going one way by ship and one way by plane. Arrangements for the Hawaiian trip are in course of preparation and details will be announced later.

A great many valuable suggestions have been received concerning postgraduate courses desired at Los Angeles, San Francisco, Berkeley, Portland, Denver, and other West Coast centers. These suggestions are under consideration by the Committee on Postgraduate Courses.

Many very helpful suggestions were also received concerning the content of the program of clinics, round tables, morning lectures, and general sessions, and those suggestions have been referred to the appropriate committee chairmen.

All members who have thus far not returned the questionnaire are urged to do so, so that adequate arrangements can be made in advance.

Captain Lloyd R. Newhouser, (MC), USN, F.A.C.P., of the Bureau of Medicine and Surgery, Washington, D. C., has been awarded the Legion of Merit for his distinguished work in developing the Navy's program for obtaining, processing, packaging and distributing plasma and serum albumin during the recent war.

Colonel Arden Freer, (MC), USA, Ret'd., F.A.C.P., presently an Executive Officer of the Veterans Administration, is a recipient of the Legion of Merit. The award recognizes Dr. Freer's exceptionally meritorious services as Chief of Medical Service and subsequently as Executive Officer, of the Walter Reed General Hospital, and as Director of the Department of Internal Medicine of the Army Medical Center.

Effective October 1, 1947, Dr. Edward L. Bortz, F.A.C.P., President of the American Medical Association and Governor of the American College of Physicians for Eastern Pennsylvania, became Honorary Consultant to the Medical Department of the United States Navy.

Dr. Allan Seymour Walker, M.D., F.R.A.C.P., the Official Medical War Historian for Australia, and the first Honorary Secretary of the Royal Australasian College of Physicians, was a visitor to the Headquarters of the American College of Physicians on October 2, 1947.

The rank of Officer of the French Legion of Honor has been conferred upon C. Charles Burlingame, M.D., F.A.C.P., Hartford, Conn., in recognition of his contributions as Chairman of the American Advisory Board for the American Hospital of Paris, and as an Officer in the Army during the recent war.

John F. Kenney, M.D., F.A.C.P., Pawtucket, R. I., has been honored by the Memorial Hospital of that city in its adoption of the title "The John F. Kenney Annual Clinic of the Memorial Hospital Internes' Alumni Association." All physicians in Rhode Island, and in nearby cities, were invited to attend the Tenth Annual Clinic on October 29, 1947.

J. C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco, has been honored with an official citation and scroll from the President of Costa Rica, and with the Presidential Medal of Merit (gold and diamond) from the President of Nicaragua.

Roberto F. Escamilla and Richard D. Friedlander, Fellows of the College in San Francisco, have recently been appointed Associate Clinical Professors of Medicine in the University of California Medical School.

The Joint Committee for the Coördination of Medical Activities, in which the College is represented by Ernest E. Irons, M.D., F.A.C.P. (Chairman) and Walter L. Palmer, M.D., F.A.C.P., met again on August 16, 1947. The discussions at this meeting have been published in full in the Journal of the American Medical Association.

A fine tribute was paid to a past President of the College on his 78th birthday when, on September 21, 1947, Dr. F. M. Pottenger, Sr., of Monrovia, Calif., received the following statement from the Board of Supervisors of the County of Los Angeles. "It is the feeling of the leaders of the County that the great work you have performed in so sharply reducing the incidence of tuberculosis places the entire community in your debt. A debt that can never be paid except in gratitude and appreciation. We know that tuberculosis is today claiming one-fifth as many lives as it did forty years ago when you began your courageous pioneer efforts in this field. In this sharp reduction your research and your leadership have played a great part."

The 1947 Assembly of the Interstate Postgraduate Medical Association of North America took place October 14–17 at St. Louis, Mo., under the Presidency of James E. Paullin, M.D., F.A.C.P., Atlanta. The following Fellows of the College were among the speakers at the Assembly: Cyrus C. Sturgis, M.D., Ann Arbor; Elliott P. Joslin, M.D., Boston; Richard B. Capps, M.D., and Leon Unger, M.D., Chicago; John A. Toomey, M.D., Cleveland; Franklin G. Ebaugh, M.D., Denver; Edward L. Bortz, M.D., and John A. Kolmer, M.D., Philadelphia; Walter C. Alvarez, M.D., Rochester, Minn.; Harry L. Alexander, M.D., Goronwy C. Broun, M.D., R. A. Kinsella, M.D., LeRoy Sante, M.D., Daniel L. Sexton, M.D., and August A. Werner, M.D., St. Louis.

J. Morrison Hutcheson, M.D., F.A.C.P., Richmond, Va., former Vice President of the College, has been awarded the Honorary Degree of Ll.D. by Hampden-Sydney College.

Samuel Waldman, M.D. (Associate), Brooklyn, N. Y., has contributed to the College Library of Publications a copy of "Gastroenterology in General Practice," by Louis Pelner, M.D., with contributions from others, among whom is Dr. Waldman. This book has been published recently by Charles C. Thomas, Springfield, Ill.

The Medical Society of the State of Pennsylvania offers this year a new departure in refresher courses for general practitioners: a course designed to minimize expense, travel time and interruption of practice. The Society's Committee on Graduate Education, of which Charles W. Smith, M.D., F.A.C.P., Harrisburg, is Chairman, and which includes Robin C. Buerki, M.D., F.A.C.P., Thomas M. Durant, M.D., F.A.C.P., Robert A. Matthews, M.D., F.A.C.P., and Francis C. Wood, M.D., F.A.C.P., all of Philadelphia, has secured a faculty of 150 teachers, largely from medical schools in the state, and outlined a series of ten full-day sessions in each of six cities: Allentown, Harrisburg, Johnstown, Oil City, Wilkes-Barre and Williamsport. These cities, lying across the northern and southern tiers of Pennsylvania were selected also for

their accessibility to physicians remote from the larger medical centers. In each city a day is devoted to each of the following subjects: Neuropsychiatry, Respiratory Diseases and Anesthesiology, Gastro-enterology, Urology, Gynecology and Obstetrics, Cardiovascular Diseases, Skeletal and Muscular Diseases, Skin Diseases and Nutrition, Hematology and Metabolic Disorders, Febrile Diseases and Endocrinology, Modern Therapy. Physiological and pharmacological viewpoints are emphasized. Each course begins in October and ends in May. A topic given in one city on a certain weekday will be repeated in another city on a different weekday, and a registrant may attend the session when and where it is most convenient for him to do so.

Retirements from Service

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to October 15, 1947 inclusive).

Samuel M. Browne, Anderson, S. C. (Col., MC, USA)
Frederick H. Foucar, New York, N. Y. (Col., MC, USA)
Gustavus A. Peters, Rochester, Minn. (Major, MC, AUS)

OBITUARIES

DR. HORACE WOODWARD CARLE

Horace Woodward Carle, M.D., F.A.C.P., of St. Joseph, Mo., died on April 27, 1947, of pulmonary embolism, chronic heart disease and pneumonia.

Dr. Carle was born at Cincinnati, Ohio, September 22, 1889. He attended school in St. Joseph and was active there in athletics, drama and music. He obtained the degree of Doctor of Medicine in 1914 from the Loyola University School of Medicine and interned at the Kansas City General Hospital. Dr. Carle entered the practice of medicine in St. Joseph in 1915 and shortly thereafter limited his practice to internal medicine. He was a local pioneer in the use of clinical laboratory methods and was recognized as an outstanding leader in his field. Dr. Carle served on the staffs of the Missouri Methodist and St. Joseph's Hospitals, and was a past president of the staff of the former hospital.

A Fellow of the American College of Physicians since 1934, Dr. Carle was also a Fellow of the American Medical Association and a member of the Buchanan County (past president), Missouri State (vice president, 1921), and Southern Medical Societies, American Heart Association and the Kansas City Southwest Clinical Society.

Dr. Carle was a member of the Missouri State Board of Health and Medical Examiners, 1928–32, and president, 1931–32. He served for twelve years on the St. Joseph School Board, and was at one time its president.

DR. EDWARD L. HANES

Edward L. Hanes, M.D., F.A.C.P., died July 14, 1947, at Altadena, Calif.

Dr. Hanes was born at Chenango Forks, N. Y., in 1871. He graduated from The Albany Medical College in 1899 and served his internship at the New York Lying-in-Hospital. He served on the staff of the Craig Colony for Epileptics, at Sonyea, N. Y., the Hudson River State Hospital, at Poughkeepsie, N. Y., and was a member of the medical staff of the Rochester State Hospital until 1909 when he entered private practice in Rochester. Dr. Hanes was on the consulting staff of the Rochester General Hospital and attending neurologist at St. Mary's Hospital and the Genesee Hospital. During World War I, Dr. Hanes, with rank of major, was in charge of the Neuropsychiatric Division Base Hospital 19, serving overseas. He later served as consultant in neuropsychiatry for the Veterans Administration, and was on the consulting staff of the Rochester State Hospital and of the Craig Colony.

Dr. Hanes was a member and former president of the Rochester Academy of Medicine, and a member of the American Psychiatric Association, Medical Society of the County of Monroe, and the Rochester Pathological Society. Early active in the prevention of mental disease, he was largely responsible for the establishment of the first Mental Hygiene Society in Rochester. He was frequently called upon to testify in important legal trials. Among his publications was a volume, "The Minds and Nerves of Soldiers," in which he reviewed his experiences in World War I.

A founder of the Neuron Club, Dr. Hanes was active in its formative days. A kindly gentleman maintaining the highest ideals of our profession, Dr. Hanes had the respect of all those who knew him.

EDWARD C. REIFENSTEIN, M.D., F.A.C.P.,
Governor for Western New York

DR. FRANCIS EDWARD HARRINGTON

Francis Edward Harrington, M.D., F.A.C.P., died at West Palm Beach, Fla., May 9, 1947. Dr. Harrington was born at Norfolk, Va., June 19, 1879.

A graduate of Gonzaga College, Washington, D. C., Dr. Harrington completed his medical course at the George Washington University School of Medicine in 1904. He then engaged in medical practice and served as part time medical inspector in the Health Department, Washington, D. C., from 1904 to 1910. He was Health Officer of Cumberland, Md., from 1910 to 1914. During the following seven years Dr. Harrington served as Epidemiologist in the U. S. Public Health Service. In 1920 he became Commissioner of Health, Minneapolis, Minn., and in 1921 Director of the Lymanhurst Health Center. Dr. Harrington held appointment in the University of Minnesota Medical School, 1938 to 1945, as Clinical Professor of Preventive Medicine and Public Health, and, from 1945 to 1947, as Clinical Professor Emeritus of that subject.

He had been Vice President of the American Public Health Association and of the American Association of School Physicians, and Secretary of the International Society of Medical Health. He was a member of the Hennepin County Medical and Public Health Associations, the Minnesota State Medical Association, National Tuberculosis Association, Association of Military Surgeons, and a Fellow of the American Medical Association and American College of Physicians.

Dr. Harrington was noted for his kindliness in all his relationships with his colleagues and especially for his interest in caring for the welfare of internes and residents in the Minneapolis General Hospital. He was a vigorous fighter for what he thought was right in hospital management and in public health work. One of his major interests was in the detection and prevention of the spread of tuberculosis in the population of Minneapolis. It was for these reasons that he established the Lymanhurst Health Center and fought vigorously for its maintenance and support, often against strong opposition. The recent x-ray survey for tuberculosis in the population of Minneapolis showed a very low incidence of active pulmonary tuberculosis. This excellent result is owing largely to the efforts of Dr. Harrington. As a result of his death his colleagues and friends have lost a fine gentleman and esteemed physician.

EDGAR V. ALLEN, M.D., F.A.C.P.,
Governor for Minnesota